The neuroanatomy of working memory in treatment resistant schizophrenia an integrative approach

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The Neuroanatomy of Working Memory in Treatment Resistant Schizophrenia: An Integrative Approach

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To my parents,

Rowland and Kathlyn Presdee

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Abstract

This thesis concerns an under-researched and, until recently, neglected category of schizophrenia described as "Treatment Resistant Schizophrenia" (TRS). This applies to individuals who have not clinically responded to at least two trials of chemically different antipsychotics, at an adequate dose and duration, yet respond to clozapine. This unique drug has, potentially, many therapeutic actions and is notable for its lack of extra-pyramidal side effects associated with antagonism at the Dopamine (D2) receptor - the target of conventional antipsychotics. Consequently, the fundamental question pervading research in this area is whether TRS represents a distinctive aetiopathological category or whether it reflects greater illness severity?

Epidemiological research indicates TRS may affect around 21% of individuals with schizophrenia, therefore, there is an urgent need to study the neurobiological substrates of TRS to facilitate identification and optimal treatment.

AIMS AND HYPOTHESES:

The primary aim of this research was to characterize TRS through clinical assessment, neuropsychological tests and an exploration of task evoked changes in the blood-oxygen-level-dependent (BOLD) signal at different levels of cognitive load during a verbal n-back working memory task, using functional magnetic resonance imaging along with the exploration of the association between the BOLD signal and clinical correlates.

It was hypothesised that:

1) TRS individuals would show attenuated engagement of an "executive" fronto-parietal network during working memory processing compared to controls.
2) Brain areas exhibiting altered haemodynamic response would include the cingulate gyrus and would be associated with task performance and symptom severity.

Secondary aims included the exploration of the association between clinical and cognitive variables and between BOLD signal, clinical and cognitive outcome measures.

METHODS:

Twenty-six individuals with TRS, medicated with clozapine, and 21 healthy control participants performed a verbal n-back working memory task in a 3-Tesla GE Signa Neurovascular MR system. This task had three levels of cognitive load (1-, 2-, 3-back). TRS participants were assessed with the Positive and Negative Syndrome Scale (PANSS) to

measure symptom severity, the Wechsler Abbreviated Scale of Intelligence (WASI) and MATRICS Consensus Cognitive Battery (MCCB). Functional MRI data were analysed using XBAM_v4.1 software which uses a non-parametric approach. The interaction of group and task condition (cognitive load) was explored using ANCOVA. Groups comprised: a) TRS participants and controls; b) TRS divided according to PANNS scores (lower PANNS: median total score=41; higher PANNS: median total score=66). Age was a covariate in all imaging analyses.

RESULTS:

The group with the higher level of pathology (TRS participants relative to controls) displayed attenuated haemodynamic responses with increasing cognitive load in the right middle frontal gyrus and left frontal gyrus, left middle temporal gyrus and parahippocampal gyri bilaterally, the right thalamus, right parietal lobe, right precuneus and left lingual gyrus. They also showed increased haemodynamic responses in the left superior/medial frontal gyrus, left cingulate (anteriorly and posteriorly), the right putamen and left paracentral lobule.

Similarly, the higher PANSS group exhibited an attenuated haemodynamic response with increasing cognitive load in the left claustrum and left frontal gyrus relative to the lower PANSS group, as well as increased haemodynamic responses in left superior frontal, right medial frontal and right postcentral gyri.

The behavioural and neuropsychological analyses in the TRS group revealed estimated IQ scores clustered around the peak of the normal distribution yet scores on the MCCB tests were consistently depressed relative to standardisation norms for the general population. Also, scores were superior in the lower PANSS group on the speed of processing composite, the test of visual learning, and for attention and vigilance, all at trend level significance. Further, exploratory correlations revealed negative symptoms were strongly associated with decrements in attention and with estimated full-scale IQ and verbal IQ scores.

CONCLUSIONS:

Clozapine can ameliorate long-standing symptoms in TRS and has been demonstrated to have a wide range of biological effects. This study showed that with increasing working memory load there was a pattern of attenuation in the haemodynamic response during the working memory task in the groups with the higher level of pathology (i.e. TRS relative to control participants and higher PANSS relative to lower PANSS participants) which implicated “connector hubs” which is suggestive of a pathology affecting long range

communication. The altered haemodynamic response included brain areas which are part of an “executive” network as well as a “default mode network”. This pattern of activity might reflect hyperactivity in the default mode network undermining activity in the cognitive control fronto-parietal executive network, possibly through microlapses in attention.

At a cognitive level, the lower PANSS group performed better than the higher PANSS group on tests of learning and attention. On the basis of these findings, a tentative conclusion is proposed that clozapine may help to restore function in the prefrontal cortex and other areas involved in working memory and further aspects of higher cognition. The results are subject to qualification by several limitations including participant selection, the likelihood that lower vs higher PANSS comparisons may be under-powered and the cross-sectional design of the study. In spite of these limitations, this study provides a framework that may contribute to understanding the neuroanatomical alterations associated with TRS.

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Abbreviations and Definitions

1H-MRS: Proton magnetic resonance spectroscopy - a neuroimaging method that enables the measurement of metabolite concentrations in a noninvasive way.

ACC: Anterior Cingulate Cortex.
Forms part of the medial wall of the frontal lobe and lies medially to the dorsolateral prefrontal cortex and superiorly to the corpus callosum which it follows anteriorly around the curve of the genu to the rostral area below.

ADHD: Attention deficit hyperactivity disorder.

AST: Associative Striatum.
Lies within the pre and post-commissural areas of the caudate and putamen, not readily localised, rather it is defined by its cortical afferents associated with higher cognition, especially the dorsolateral prefrontal cortex (DLPFC), a major hub of striatal-thalamo-cortical circuity which also integrates inputs from other parts of the limbic system, which include the hippocampus, amygdala, thalamus and hypothalamus.

CPT: Continuous Performance Task; CPT-DS (degraded stimuli version); CPT-IP (identical pairs version); CPT-X (is it' X'?)

CATIE: Clinical Antipsychotic Trials of Intervention Effectiveness. Conducted at 57 sites this study compared the efficacy of atypicals compared with a first-generation antipsychotic in chronic schizophrenia as measured by any/all-cause discontinuation rates over an 18-month period.

Conventional Antipsychotics: also known as "first generation", "neuroleptic medication", "typicals." medication which have clinical efficacy through antagonism at the dopamine D2 receptor. Clozapine may also be described as a first generation antipsychotic but has atypical actions.

CAR: Cortisol awakening response - a sharp increase in cortisol associated with awakening.

D1 Receptor: Dopamine D1 Receptor; D2 Receptor: Dopamine D2 receptor, etc.

DA: Dopamine.

DLPFC: Dorsolateral Prefrontal Cortex.

DMN: Default Mode Network

DS-CPT: Degraded stimulus version of a continuous performance task.

DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, 2013.

DUP: Duration of untreated psychosis. Criteria vary but usually refers to the period from the onset of symptoms during the prodrome before diagnosis.

EOS: Early onset schizophrenia.

EPSE: Extra-pyramidal side effects.

FA: fractional anisotropy - a measure of white matter integrity.

FEP: First episode of psychosis (usually the first admission of psychiatric hospital).

FLRS: First Line Responsive Schizophrenia- a term borrowed from Anderson et al., 2015, to differentiate individuals who clinically respond to first line antipsychotic treatments.

fMRI BOLD signal: Functional magnetic resonance blood-oxygen-level-dependent signal exploits differences in magnetic susceptibility of oxyhaemoglobin and deoxyhaemoglobin to provide a measure of oxygen delivery to local neural tissue

GABA: Gamma-aminobutyric acid is the major inhibitory neurotransmitter of the mammalian central nervous system.

GAD: Glutamic acid decarboxylase synthesises GABA from glutamate. The isoform GAD65 concentrated around the synapses is transiently active. GAD67 which produces most of the GABA in the brain is constitutively active and is more widely distributed in neurons (e.g. in the cytosol and around axons).

GM: Grey matter.

HVA: Homovanillic acid.

HVLT-R: The Hopkins Verbal Learning Test - Revised™.

MAM: mitotoxin methylazoxymethanol acetate is used in a rodent developmental model of schizophrenia. Administered to a pregnant rat on gestational day 17 this stimulates a maternal immune response and a schizophrenia-like phenotype in offspring which emerges around puberty.

MCCB: The MATRICS Consensus Cognitive Battery.

MDMA: 3,4-Methylenedioxymethamphetamine (Ecstasy).

NMDA / NMDAR: N-methyl-D-aspartate receptor. An ionotropic glutamate receptor which will only admit (chloride) ions if the cell bearing the receptor is in a depolarised/ firing state as this removes a magnesium block from the ion channel.

NAA: Cr ratio: N-acetylaspartate: Creatine. NAA is a marker of neuronal integrity and associated with lipid synthesis for myelination and, possibly, mitochondrial energy production.

NAc (Nucleus Accumbens)/ Ventral Striatum: A key part of the circuitry mediating reward. The NAc lies medial to the caudate, and rostral to the preoptic area of the hypothalamus where it "leans against" the septum. Haber (2016) describes the NAc as being part of ventral striatum. It is also part of the amygdaloid complex.

PCC: posterior cingulate cortex - comprises several areas (Vogt and Laureys, 2005, 2006); can include the precuneus (e.g. Andrews-Hanna et al., 2014; Leech et al. (2011).

PCP: phencyclidine.

PD: Parkinson's disease.

PET: Positron Emission Tomography.

PIQ: Performance IQ.

PPI: Pre-pulse inhibition.

PVI and **PV$^+$**: Parvalbumin containing interneurons. PV$^+$ stain positively for parvalbumin, a calcium binding protein expressed by fast spiking interneurons (a sub-category of interneuron).

PFC: Prefrontal cortex - frontal cortex anterior to the agranular cortex of Brodmann area 6 and parts of the paracentral gyrus.

PSZ: People with schizophrenia, i.e. the wider population, not necessarily including TRS.

RCT: Randomized control trial.

rsfcMRI or rs MRI: resting state functional connectivity MRI.

ROI: Region of interest.

ROS: Reactive Oxygen Species are negatively charged molecules (free radicals).

SGAs: Second generation antipsychotics.

SSQs: Sum of squares. This is a goodness of fit statistic calculated at each voxel which indexes differences in the haemodynamic response from baseline for each of the levels of task difficulty. It consists of the ratio of the sum of squares of deviations from the model time series mean divided by the sum of squares of deviations from residuals. The null distribution of SSQs assumes no response due to the experiment, is then tested using the wavelet permutation method which is described by Bullmore et al. (1999, 2001).

Striatum: The component nuclei of the striatum vary across texts, but the term literally means "striped body" which provides an apt description of the white fibres of the external capsules which largely divide the main components, the caudate and putamen on the superior aspect. Small white fibres ("Wilson's pencils") also traverse the area towards the globus pallidus. The dorsal striatum comprises the caudate and putamen, while the ventral striatum comprises the nucleus accumbens and olfactory tubercle. Striatal structures are packed with medium spiny projection neurons, the combined effect of which is to provide a

major GABAergic inhibitory drive to the thalamus via direct and indirect pathways as described in Haber (2016).

SPECT: single-photon computerized emission tomography

TNN: task negative network - "identified on the basis of both spontaneous correlations within each network and anticorrelations between networks" using resting state functional connectivity MRI (Cauda et al., 2010).

TPN: task positive network.

TRS: Treatment resistant schizophrenia.

Typicals: Also known as "first generation" antipsychotics or "conventional neuroleptics." These drugs are antagonists at the dopamine D2 receptor.

UFM: Unaffected family member who is a first-degree relatives of an individual with schizophrenia.

U-TRS: Ultra-treatment resistant schizophrenia (where individuals do not clinically respond to typical, atypical antipsychotics or clozapine at an adequate dose or duration).

VENs: von Economo or "spindle neurons" found at high density in the core nodes of the salience network (ACC and insula; also in the DLPFC).

VIQ: Verbal IQ.

VLPFC: Ventrolateral prefrontal cortex.

vmPFC: Ventromedial prefrontal cortex.

VTA: Ventral Tegmental Area: lies on the ventral surface of midbrain around midline and contains a large population of dopaminergic cells which receives afferents from the hippocampus and brainstem and projects to the striatum.

WM: Working memory.

Some Network Terminology

Betweenness centrality: In graph theory this is a measure of how frequently an area is used to communicate with another, so it also indicates the importance of a hub in the optimal organisation of pathways. Therefore, "connector hubs" have high betweenness centrality. Prime examples are the ACC and insula which form the salience network

LFP: **Local Field Potential: "**electric potential generated in a volume of neural tissue by a local population of neurons. LFPs result from the flow of current in the extracellular space generated by electromotive forces operating across the cell membranes of neurons, principally at synapses" - Bressler and Menon (2010)

SCP: Slow cortical potential: a local field potential with slow oscillatory activity for example, in the delta band - which correlates with fMRI BOLD measures in the resting state (Raichle, 2009).

Task positive activity: involves outwardly directed attention, as opposed to "**task negative activity**" involving internal mentation such as day-dreaming, self-reflection, planning and the prospective use of memory associated with DMN activity.

Chapter I - INTRODUCTION

1.1 The Burden of Schizophrenia

Schizophrenia is a devastating disorder which, for many, has an onset during adolescence or young adulthood, blighting the prospects of young lives. This is evidenced by a high risk of suicide, which was reported to be 8.5 times higher than might be expected in western populations (Harris and Barraclough, 1997). While, more recently, an epidemiological study of a cohort of 8624 individuals with schizophrenia from the Danish national register by Wimberley et al., 2016, revealed especially high levels of suicide attempt associated with treatment resistant schizophrenia (TRS) at 27 - 30% (depending on the definition) and 15% for other categories of schizophrenia.

Individuals with schizophrenia are also more likely to die at a younger age from physical illnesses which, at first sight, appear to be unrelated to schizophrenia or its treatment (McGrath et al., 2008; De Hert et al., 2011). The adverse social and economic impact of chronic and disabling illness seems an inadequate explanation, although a higher prevalence of smoking could be a contributory factor (Salokangas et al., 2006).

Schizophrenia has been ranked by the World Health Organisation as one of the top ten illnesses that contributes to the burden of disease (Murray and Lopez 1996). In one systematic review covering 46 countries, regional estimates of the lifetime risk ranged from 0.3 - 2.0%, with an average of 0.7% (Saha et al., 2005). This variation may partly reflect differences in diagnostic criteria, however, an examination of the incidence of new cases by Tandon et al. (2008) pointed to urbanisation, migration and industrialisation contributing to higher rates. They suggested increased exposure to environmental toxins, disease, vitamin D deficiency, poverty, access to drugs of abuse and a loss of social support as possible factors. Moreover, all these may negatively impact upon maternal health and the prenatal and perinatal health of children, which might also affect the prevalence of schizophrenia which is now widely considered to be a neurodevelopmental disorder (Murray et al., 2017).

1.2 The DSM-5 Definition of Schizophrenia

The highly influential diagnostic manual of the American Psychiatric Association, DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, 2013) has recently made a number of important changes concerning the diagnosis of schizophrenia. It is now stipulated that an individual must have experienced at least two symptoms, from a list of five, for a minimum of a month: delusions, hallucinations, disorganised speech,

disorganised or catatonic behaviour, or negative symptoms. Also, at least one of the symptoms should be from the first three "positive" items in the list. The severity of symptoms is also considered and there is an expectation of deterioration from premorbid function, or underachievement where onset arises during childhood or adolescence. Further, some symptomatology, with deterioration in occupation or social function must be present for at least 6 months, albeit in attenuated form, but including one month of "active symptoms - shorter if responsive to treatment. Alternative illnesses should be ruled out[1]. Tandon, et al. (2013), commented cognitive symptoms are a common feature, however they are not diagnostic of schizophrenia and so were not included in DSM-5).

DSM-5 has also firmly placed the diagnosis of schizo-affective disorder within schizophrenia by requiring that individuals must meet the criteria for schizophrenia first before an affective component is added. Another important change is the removal of longstanding sub-categories: "paranoid", "disorganized", "catatonic", "undifferentiated", and "residual type" as they were deemed by the American Psychiatric Association (2013) to have "limited diagnostic stability, low reliability, and poor validity." More fundamentally, the abandonment of categories may reflect disillusion with the way this complex disorder has been conceptualised. However, there may still be a case for sub-categories and this thesis sets out evidence which suggests the future inclusion of TRS as a sub-category could be an important step for research purposes and have implications for diagnosis and treatment. First, as relatively few studies have specifically addressed TRS, this needs to be set within a broader context of schizophrenia research.

1.3 A Diversity of Symptoms

Schizophrenia has many manifestations involving a heterogeneous range of symptoms where no individual symptom is necessary or sufficient for a diagnosis. However, the classification of some symptoms as "positive" or "negative" has proved useful. Briefly summarised, positive symptoms describe an "excess" of behaviour or perceptions, such as hallucinations and delusions, whereas negative symptom suggest a deficit, for example, "alogia", "anergia", "avolition." These ideas were the basis of scales developed by Crow (1980) and Andreasen (1982, 1989) which were later incorporated into the 30-item Positive and Negative Syndrome Scale (PANSS) which comprises three subscales: positive, negative and general (Kay, Opler, and Lindenmayer 1987; Kay, Opler, and Lindenmayer

[1] Steiner et al. (2013; 2014) observed some individuals with antibodies to the N-methyl-D-aspartate receptor (NMDA receptor or NMDAR) "with disorganized and catatonic features of schizophrenia may be misdiagnosed encephalitis cases", p. E6.

1988). Moreover, there appears to have been an early consensus that positive symptoms may be associated with excessive dopamine release in the striatum during active psychosis (Sartorius et al., 2009).

However, the basis of negative or "deficit" symptoms has been less clear, i.e. there may not be a simple correspondence with insufficient dopamine function. Initially, Kay et al. (1988) suggested scores on the positive and negative scales might be anti-correlated. However, this has not been supported, possibly because the items may reflect more than one dimension (Blanchard and Cohen 2006). Indeed, just as the classification of symptoms in the DSM-5 has not been without debate, Kay et al. (1988) may have struggled, describing some symptoms as "secondary negative" (e.g. disturbance of volition, motor retardation, poor attention, preoccupation and depression). These were assigned to their general scale. Similarly, "excitement" was not classified as a positive symptom but put in the general scale on the basis it reflects arousal.

There is now more empirical evidence to support symptom dimensions and potential biological substrates than was available to Kay et al. (1998) and it seems the general scale reliably disappears in factor analyses and not all the items are retained. An analysis of 29 published studies by Wallwork et al. (2012) indicated factor analysis of symptoms in the PANSS generally yields 5 factor solutions instead of 3 (summarised in Table 1. 1 below). One of the more overtly cognitive items from the negative scale, "conceptual disorganisation", which relates to impairment in abstract/symbolic forms of thinking, i.e. beyond sensory-motor representations, was reclassified into a new "disorganized/ concrete factor". Another negative item, "stereotyped thinking", disappeared entirely. Also, "attentional impairment", which was described as a negative factor in a personal communication from Andreasen to Kay (Kay et al., 1988) but assigned to the PANSS general scale (G11), emerged as a cognitive symptom under the disorganized/ concrete factor. Further new factors "excited" (comprising poor impulse control, poor attention and hostility) and "depressed", were self-explanatory. Just four items were retained on the positive scale: "delusions", "hallucinatory behaviour", "grandiosity" with the further addition of "unusual thought content" (formerly, G9 on the general scale). This last item includes symptoms with a bizarre aspect (sometimes referred to as "passivity phenomenon"), such as "thought broadcast" and "thought insertion"[2].

[2] Potentially, just as auditory hallucinations have been proposed to arise from misattribution as to the source of auditory stimulation, a similar explanation might apply to thought insertion and thought broadcast. The faulty use of feedback against expectation ("prediction error") provides a possible explanatory mechanism (Shergill et al., 2005; Tracy and Shergill, 2013; Friston, 2016).

Table 1. 1 A 5-factor model of the Positive and Negative Syndrome Scale - based on a confirmatory factor analysis of 29 models by Wallwork et al. (2012)

POSITIVE
P1 Delusions P3 Hallucinatory behaviour P5 Grandiosity G9 Unusual thought content
NEGATIVE
N1 Blunted affect* N2 Emotional withdrawal N3 Poor rapport N4 Passive/apathetic social withdrawal N6 Lack of spontaneity & flow of conversation* G7 Motor retardation
DISORGANIZED/ CONCRETE FACTOR
P2 Conceptual disorganisation N5 Difficulty in abstract thinking G11 Poor attention
EXCITED
P4 Excitement P7 Hostility G8 Uncooperativeness G14 Poor impulse control
DEPRESSED FACTOR
G2 Anxiety G3 Guilt feelings
(Codes on left represent item numbers on the PANSS Scale (Kay et al., 1987): N = Negative, P = Positive, G = General item). * Subcategory: “diminished emotional expression” (Hartmann-Riemer et al., 2015).

Looking across a selection of studies (including, Nunnally and Bernstein 1994; Rodriguez-Jimenez et al., 2013), positive, negative and “cognitive” dimensions endure, however, items under the cognitive dimension vary considerably (Honey et al., 2003). The most stable items on the PANSS scale are those on the negative subscale as they undergo the least attrition and reassignment, for example, in Wallwork et al.’s model, 5/7 items (blunted affect, emotional withdrawal, poor rapport, passive /apathetic social withdrawal, lack of spontaneity and flow of conversation) were joined by “motor retardation” from the general scale. Notwithstanding challenges in classifying a heterogeneous range of symptoms, the PANSS has been widely used and remains a valuable research tool (for example, in a multi-centre study, Glick et al. (2015), found a reduction of 10 points in total PANSS scores translated to sizeable reductions in the length of hospitalisation). As such the PANSS was selected for this study (Methods, section 2.6).

1.4 Epidemiology

1.4.1 Outcomes and Age of Onset

Fortunately, not everyone who develops schizophrenia will have further episodes of psychosis and deterioration is not inevitable, for example, in one prospective study over 15 years, more than 50% of affected individuals did not have a course of schizophrenia that was "chronic or continuous" (Harrow et al., 2005). A meta-analysis of studies by Lally et al. (2017), relating to more than 12,000 individuals (including some with an affective psychosis) revealed remission rates after a first episode of psychosis (FEP) of around 58% at an average follow-up of 5.5 years. Further, a cross-sectional study of prescribing practices for 5055 individuals with schizophrenia and schizo-affective disorder in England and Wales, estimated that 21.4% of individuals were in full remission and 50.2% were in partial remission with minimal symptoms. However, 28.4% were not in remission or still had substantial symptoms or disability (Patel et al., 2014).

These observations provide a welcome correction to the impression that schizophrenia has a relentlessly bleak prognosis. Importantly, Zipursky et al. (2013) have proposed where illness does progress this could be due to a lack of appropriate treatment, social and financial poverty, so "mental health professionals need to join with patients and their families in understanding that schizophrenia is not a malignant disease that inevitably deteriorates over time but rather one from which most people can achieve a substantial degree of recovery." (p.1363)

Nonetheless, relapse, or the persistence of certain symptoms are major problems and epidemiological studies have identified subgroups; for example, one study of medical records in the Israeli population over three decades identified 2290 individuals with schizophrenia from a cohort of all those born between 1970-1988 and revealed four different trajectories based on the annual average number of days in hospital (Levine et al., 2011). The largest group (57%) had a mean age of onset of 20 years and spent an average of 44 days in hospital upon first admission and 48 on the last. While another group comprising 15.5% had a first admission at the mean age of 17.1 years. The trajectories of both groups revealed substantial recovery by the age of 23 years. (A similar stabilisation was observed by Lally et al. (2017). However, 12% of the cases in Levine et al. (2011), had a mean age of onset around 18 years and a progressive course indicated by lengthening periods of hospitalisation. Their fourth group was characterised by a later age of onset (mean 29 years) and comprised a significantly higher proportion of males (72.7%), although it was observed this may have changed with an extended age range.

1.4.2 Sex Differences

This is quite possible as the distribution of onset for women is markedly different, with a later and broader range of onset (Abel, Drake and Goldstein 2010; Aleman, Kahn, and Selten, 2003). Interestingly, there may be an increased incidence around major hormonal changes such as puberty, childbirth and the menopause, even across the menstrual cycle (Riecher-Rossler et al., 1994; Markham, 2012). Associations between cognitive impairment and menstrual irregularity (or post-menopause) have also been reported, for example, in a sample of 242 healthy women by Gurvich et al. (2018), bolstering conjecture that some neural protection may be afforded by female sex hormones which are also synthesised in the brain as neurosteroids (Seeman 1997; Hafner et al., 1991), during development and in the mature brain (Cutter, Norbury, and Murphy 2003). In one study, peak bone density (used as a marker of lifetime exposure to estrogen) was one standard deviation lower in women with schizophrenia compared with a control group matched for education, age and other characteristics (Maric et al., 2005).

At least two estrogen hypotheses of schizophrenia has been proposed - as reviewed by Hayes et al. (2012): one emphasises the potentially protective effects of estrogen and related sex hormones, while the other proposes a deficiency. More specifically, Hayes et al. (2012) referencing Adams et al. (2004), observed "Oestradiol is known to upregulate NMDA receptors, change their subunit configuration, and increase NMDA agonist binding in the rat brain, which could presumably help reverse hypoactive glutamatergic functioning in schizophrenia." (p.3)[3]

The dopamine system may also be affected, for example, in one preclinical study, Chavez et al. (2010), demonstrated that following ovariectomy, estrogen treatment could completely reverse consequent decrements in the dopamine transporter DAT and changes in the density of D2 receptors in the nucleus accumbens and caudate nucleus, while leaving serotonergic aspects unaffected.

It is also interesting that the only drug with superior efficacy for TRS, clozapine, has been shown to greatly increase the neurosteroid and sex hormone pregnenolone in the rat hippocampus (Marx et al., 2006). Pregnenolone has been described as being neuroprotective and enhancing "learning and memory, myelination, and microtubule polymerization" and, potentially, may also have downstream effects at GABA-A and NMDA receptors (Marx, 2014). The use of pregnenolone as an adjunctive treatment for

[3] N-methyl-D-aspartate receptor, or NMDAR.

schizophrenia was further explored in a randomised control trial (RCT) in a study of 120 individual receiving first or second-generation antipsychotics. After 8 weeks, improvements in functional outcomes were observed in the pregnenolone group relative to placebo, yet without cognitive improvement. Nor were negative symptoms ameliorated, however, they were low at baseline (Marx et al., 2014), but another RCT by Ritsner et al., 2014 did report significant benefit. Also, cognitive improvements, including visual attention, were observed in a small RCT by Kreinin et al. (2014).

Group characteristics, including symptoms at baseline and the type of adjunctive medication, dosage and duration could all help to account for differential findings. In another RCT of 12 weeks duration by Kulkarni et al. (2015) using raloxifene hydrochloride (a "selective estrogen receptor modulator" to prevent osteoporosis), reported significant reductions in symptom severity in their group of 56 individual with treatment refractory schizophrenia or schizo-affective disorder. Emerging evidence therefore suggests the actions of sex steroids could cast some light on the pathophysiology of schizophrenia and be used as adjunctive medication.

1.5 Can schizophrenia be treated? The discovery of antipsychotics

Although a biological basis for schizophrenia seemed apparent to Kraepelin, who identified and described the illness as a dementia of youth (1887), there was a long period during the last century when psychological theories were to the fore, as exemplified by the judgemental sounding notion of the "schizophrenogenic mother" which gained currency during the 1970's (Harrington, 2012; Neill, 1990). By that time however, the first antipsychotic, chlorpromazine, a chlorinated phenothiazine, had been trialled in Paris after an army surgeon, Henri Laborit, had noted the calming effect of this anaesthetic. When eventually tested in psychiatric patients, it was observed to attenuate the symptoms of psychosis within just three days (Delay and Deniker 1952). Another drug, haloperidol - a butyrophenone synthesised in 1958 in Paul Janssen's laboratory as an analgesic, was observed in rodent studies to have similar effects to chlorpromazine (Granger and Albu 2005). Carlson and Lindqvist (1963) proposed these drugs blocked monoamine transmission, preparing the ground for van Rossum's insight that the efficacy of antipsychotics might arise from their ability to suppress dopaminergic activity (van Rossum, 1966; Madras, 2013).

In the same era, there was another serendipitous discovery when clozapine, which had been synthesised in 1958 as a tricyclic antidepressant, was found to have antipsychotic properties. According to Crilly (2007), by 1966 clozapine had been trialled in 100 individuals with

schizophrenia and in 1973 it was being marketed in several European countries. Clozapine greatly benefitted some patients who did not respond to conventional antipsychotics, or those who were developing extra-pyramidal side effects (EPSE) such as irreversible tardive dyskinesia[4]. In 1974, clinical trial data in the USA indicated clozapine could cause hypotension in healthy individuals, informing titration regimes (Honigfeld, 2005)[5]. However, progress was abruptly halted when clozapine was withdrawn from several countries in 1975 after a cluster of deaths in Finland from agranulocytosis. The pharmaceutical company, Sandoz, ended its research program the following year but continued to supply clozapine on compassionate grounds. Eventually, incentivised by legislative changes, including repatenting (Crilly, 2007), a double-blind comparison with chlorpromazine was conducted which established clozapine's superior efficacy for positive and negative symptoms in individuals "refractory to neuroleptics" (Kane et al., 1988). Clozapine was reintroduced under licence in the UK in 1990 and also in North America and is now prescribed according to a protocol which requires regular monitoring of white blood cell counts.

In the years that followed, a second generation of drugs (often called "atypicals") were developed which were partly inspired by the low liability for EPSE of clozapine. They were successful in so far as the drugs were effective antipsychotics and had different side-effect profiles from the first generation. However, an unexpected finding of a multi-centre study (the CATIE[6] trials) was that overall clinical efficacy of the four comparison drugs (as measured by "any-/all cause treatment discontinuation" was not superior to a first generation antipsychotic perphenazine which tends to cause fewer EPSE than haloperidol. Only olanzapine, chemically more similar to clozapine, had lower rates of discontinuation despite a marked liability for weight gain and other metabolic side effects (Liebermann et al., 2005; Stip et al., 2007).

[4] The margin between clinical efficacy and side effects seems quite narrow - the appearance of EPSE was regarded by some as a sign that an adequate dose had been achieved: "The more pronounced the extrapyramidal symptoms, the better the antipsychotic effect" (Crilly, 2007, pp.41, 42). In support a double-blind study of first-episode participants indicated: "The likelihood of clinical response, hyperprolactinemia, and extrapyramidal side effects increased significantly as D (2) occupancy exceeded 65%, 72%, and 78%, respectively." - Kapur, 2000.

[5] Personal interview by John Crilly, 1–2 Aug. 2005, referenced in Crilly, 2007.

[6] Clinical Antipsychotic Trials of Intervention Effectiveness.

Therefore, it seems there have been no major drug discoveries on a par with those of clozapine and the first generation. More recently, pharmaceutical companies have largely discontinued their costly investments (an account is provided in Bullmore, 2018). Nonetheless, some research initiatives continue, such as the RCTs into progesterone, estrogen, related hormones and metabolites by Marx and colleagues mentioned above. Advances across many areas of science, including genetics are also facilitating integrative and systems approaches to understanding schizophrenia, which may lead to better treatments.

1.5.1 The Dopamine Hypothesis - "the fuel that stokes the psychotic fire"[7]

Support for van Rossum's idea (1966) that dopamine might have an important role in the symptoms of schizophrenia came from Seeman and Lee (1975; 1995) who demonstrated an impressive correlation between the average doses at which various antipsychotic drugs have clinical efficacy and their ability to block the release of dopamine upon electrical stimulation of the rodent striatum. Further support came from observations that psychostimulants like amphetamine, which increases dopamine availability in the striatum[8], could worsen or precipitate the transient emergence of positive symptoms in individuals with schizophrenia (Laruelle and Abi-Dargham, 1999).

Hall et al. (1994) provided useful information about the distribution of Dopamine D1 and D2 receptors throughout the human brain, but observations from postmortem studies concerning the density of D2 and D2-like receptors in schizophrenia, where antipsychotics are thought to exert their main therapeutic effect (Steeds et al., 2015), have been difficult to interpret because antipsychotic treatment is known to upregulate these (Laruelle and Abi-Dargham, 1999, Muller and Seeman, 1978). However, non-invasive in vivo neuroimaging methods such as single-photon computerized emission tomography (SPECT) and positron emission tomography (PET) have provided clear evidence of dopamine dysregulation: for example, one early SPECT study that used a dopamine depletion paradigm to "unmask" receptors observed elevations in striatal D2 receptor availability (indexed by increased binding of a radioligand) in participants with schizophrenia who were either antipsychotic naïve or newly relapsed and untreated (Abi-Dargham et al., 2000). The upregulation of

[7] From Kapur (2003), echoes the imagery of Laruelle and Abi-Dargham's (1999) paper 'Dopamine as the wind of the psychotic fire: new evidence from brain imaging studies', and alludes to the intensity and, perhaps also destructive aspects of the psychotic experience. Similarly, Kay Redfield-Jamieson's (1993) book "Touched by fire" concerns creativity in people who have experienced mental illness.

[8] According to Slifstein et al. (2015) amphetamine increases synaptic concentrations by reversing the dopamine transporter. (Their ref: Sulzer D, Maidment NT, Rayport S, 1993).

receptors, relative to healthy controls, was tentatively interpreted as a sign of increased availability of synaptic dopamine, higher affinity for D2 receptors or a combination of both (p.8108). (Although upregulation might also occur where there is a lack of stimulation, as proposed by Abi-Dargham et al., 2002 concerning increases in D1 receptor in the prefrontal cortex in medication free or neuroleptic naïve individuals with schizophrenia).

Compatible with the idea that striatal hyperdopaminergia underlies positive symptoms, high baseline levels of dopamine predicted "better or faster" clinical responses. Notwithstanding the lower risk of EPSE, it was concluded D2 antagonism at an early stage is an important mode of action of atypicals, however, it was acknowledged there were some individuals who exhibited positive symptoms yet did not show alterations in dopamine levels: "In these patients, psychotic symptoms may reflect a non-dopaminergic chemical imbalance, such as a deficiency in glutamatergic function." (Abi-Dargham et al., 2000, p.8109). It is possible these participants had TRS or ultra-TRS (the latter appear non-responsive to clozapine).

Several PET studies have reported increases in the synthesis capacity of pre-synaptic dopamine in individuals acutely unwell with schizophrenia, relative to healthy controls (as described by Howes and Kapur, 2009 and Egerton et al., 2013). The methodology involves radiolabelling the dopamine precursor L-dopa and measuring its accumulation in synaptic vesicles (Hietala et al., 1995). Importantly, these findings have been extended to unaffected first-degree relatives (Huttunen et al., 2008) and individuals experiencing prodromal signs of schizophrenia (Howes et al., 2009). Moreover, in the latter study, the increase in dopamine synthesis capacity correlated positively with the severity of symptoms on the PANSS but not with measures of anxiety or depression. Negative correlations were also observed between striatal synthesis capacity and measures of semantic and phonological fluency (assumed to measure executive function)[9] indicating cognitive processes may be compromised by abnormal striatal dopamine function in the prodrome. On this point, a meta-analysis of 19 studies (Fusar-Poli et al., 2012) involving 1188 individuals at clinical high risk of psychosis, confirmed decrements in performance on tests of general intelligence and cognition across several domains with the greatest impairment being observed in relation to tests of short-term verbal and visual memory. By contrast, decrements in processing speed did not reach significance which is, perhaps, surprising if cognitive deficits are characterised by indecision or processing inefficiency, however, it is possible this may be linked with the progression of disease, indeed deficits in the volume or ultra-structure of myelin might be predicted to slow conductance speeds (Joyce, 2013).

[9] The negative correlation with phonological fluency did not survive Bonferroni correction.

Egerton et al. (2013) subsequently replicated the finding of increases dopamine synthesis capacity during the prodrome and then combined their PET data with Howes et al. (2009). This enabled the increases to be localised to the associative striatum (AST) and sensorimotor striatum but not in the limbic striatum. This was also in agreement with a prospective study by Howes et al., 2011, which again observed elevations in dopamine synthesis capacity in the AST of 30 individuals at "ultra-high risk" of developing psychosis, relative to healthy controls. Elevations were even higher in those who subsequently transitioned to psychosis.[10]

Possibly the first study localising abnormal dopamine function to the AST (Kegeles et al., 2010) compared unmedicated in-patients with healthy controls using an acute dopamine depletion paradigm and observed the highest increase in D2 receptor availability in the precommissural dorsal caudate of the schizophrenia group (as compared with the postcommissural caudate, precommissural and postcommissural putamen and ventral striatum where D2 receptor availability didn't differ between the groups). Similarly, Demjaha et al. (2012) noted the highest uptake of [^{18}F] DOPA in individuals who had responded to first line antipsychotics (FLRS) was in the AST.

The AST is defined by its reciprocal connections with cortical areas associated with higher cognitive processing, especially the DLPFC, the cortical apex and major hub of the striatal-thalamo-cortical network which also integrates inputs from other parts of the limbic system, which include the hippocampus, amygdala, thalamus and hypothalamus. Therefore, isolating striatal dysregulation to this area may advance understanding concerning aspects of cognitive dysfunction observed in schizophrenia. This circuitry has been proposed to provide a critical role in integrating diverse information flows (Haber, 2016) and is important for monitoring performance and other forms of feedback, learning, action section and adaptive behaviour (Ullsperger et al., 2014) and other aspects of executive function. The flow of information through the striatal-thalamo-cortical loops is very complex and not completely understood but Haber has made a major contribution in this area (e.g. Haber et al., 2000, Haber, 2011, Haber, 2016) and promoted the view that this circuitry permits integration at various points, which is contrary to the traditional view that the loops function to maintain segregation. One way both separation and integration may be achieved is in the iterative flow of activity through the loops, tracking across areas of the striatum (caudate

[10] Around 35% may transition to a first episode of schizophrenia within 24 months (Stone et al., 2010).

and putamen) via collaterals while retaining topological organisation of sensory inputs. In this updated view, separation is still apparent. within the traditional divisions of the striatum (limbic, cognitive and sensorimotor).

Using resting state functional connectivity MRI (rsfcMRI) seven striatal networks were estimated by selecting the 25 most correlated vertices which, for example, determined whether striatal voxels belonged to the default mode network or the motor network. Using this approach "the posterior putamen was assigned to the motor network laterally and the ventral attention network medially.....The 7-network parcellation shows that corticostriatal circuits, in particular the association circuits, couple to zones of the striatum that extend along its longitudinal extent, consistent with anatomical studies." (Choi, Yeo and Buckner, 2012, p.2250).

Kegeles et al. (2010), commenting on role of the dorsal striatum/ precommissural dorsal caudate noted it is "involved in learning, habituation, memory, attention, motivation emotion, and volitional behavior." It may have been with some irony they further observed the lack of difference between the control and schizophrenia groups in the ventral striatum also challenged the "widely-held" assumption that this area is an important target for antipsychotic action (e.g. Lidsky, 1995) and, presumably, drug design.

As noted above, an increase in synthetic capacity in the AST can precede the onset of psychosis and before antipsychotic treatment, however, psychosis is not an inevitable end-point as not everyone transitions to psychosis and presynaptic DA function may vary during the disease (Laruelle (2013). However, there may be a case for giving antipsychotic medication to ultra-high risk individuals who show elevations in dopamine synthesis capacity but there may also be hazards, for example, Jauhar et al. (2017) commented reductions in presynaptic dopamine synthesis capacity have been observed in ADHD (Ludolph et al., 2008) and also in Parkinson's Disease (Dhawan et al., 2002) - consistent with reduced dopaminergic transmission. Apart from cognitive problems, psychosis is not uncommon in both ADHD and PD (Watson and Leverenz, 2010, Levy et al., 2015, Zahodne and Fernandez, 2008) so it is suggested here this spectrum of conditions, including schizophrenia, might possibly be associated with the inverted-U shape of dopamine function whereby optimal function is achieved when dopamine is neither too high nor too low (similarly, see section 1.5.5 on synaptic plasticity).

One of the most recent chapters in the dopamine hypothesis concerns the unexpected observation of *hypo*-dopaminergia in regions outside the striatum in drug naïve or drug-free

individuals with schizophrenia relative to healthy controls (Slifstein et al., 2015). Indeed, relatively blunted DA release was observed across all 14 preselected regions of interest: in the DLPFC, orbitofrontal cortex, medial frontal cortex, anterior cingulate and subgenu of the cingulate; also, the insula, parietal cortex, temporal cortex and occipital cortex; and subcortically, in the amygdala, hippocampus, substantia and ventral tegmental areas, thalamus and uncus. Moreover, when the percentage changes in dopamine binding potential were regressed onto fMRI BOLD activation during a working memory task performed by the same participants, it was apparent amphetamine-induced dopamine release in the DLPFC correlated positively with the magnitude of the fMRI BOLD signal, to the same degree in both the healthy controls and schizophrenia participants, although the intercept of the line of best fit was lower in the schizophrenia group indicating lower amounts dopamine were released. In addition, there was a positive correlation between baseline levels of dopamine in the DLPFC and working memory performance at higher levels of cognitive load in the healthy control group which was not present in the schizophrenia group (where perhaps maximum sensitivity to dopamine had been achieved already). Moreover, this pattern extended to the other regions of interest analysed. Slifstein et al. (2015) proposed the availability of D1 receptors in the PFC may modulate working memory performance.

It is further observed here that an analogy might be made between hypodopaminergia and blunted release of hormones following excessive activity as might, for example, following the chronic and sustained release of cortisol in Cushing's which may produce long-term changes such as reductions in hippocampal volume and reductions in the grey matter of the anterior cingulate cortex (ACC) (Andela et al., 2013, 2015), this may also affect resting state connectivity (van der Werff, 2015). Similarly, abnormalities have been observed in pituitary volumes in association with psychosis (Pariante, 2004, 2008; Garner et al., 2005, 2009). Evidence of hormonal dysregulation is apparent in the blunted release of cortisol during the first hour of waking (CAR) which has been observed in individuals at high risk of psychosis (Day et al., 2014) and unaffected first-degree relatives which was interpreted as a possible genetic predisposition towards HPA hyper-responsiveness (Mondelli et al., 2008). If the co-release of dopamine and cortisol may support cognition, then hormonal dysregulation could weaken this link, possibly contributing to the observations of Slifstein et al. (2015). A downregulation in dopamine release might occur for other reasons so it does not necessarily follow an endocrine explanation underlies their result. Yet it might, for example, if it is further considered that interactions between immune, endocrine and central nervous system are orchestrated by the hypothalamus, a collection of nuclei at the base of the brain, (Herman and Cullinan, 1997; Silverman and Sternberg, 2012). Not only are hormones released into the circulation from the pituitary to reach target glands such as the

thyroid and adrenal glands, they are synthesised within the brain where there are some direct connections, including a very strong connection from the lateral hypothalamus to the ventral tegmental area (VTA), Tyree and de Lecea (2017). Further, there are close links between the immune, endocrine and central nervous system which may be relevant to the pathophysiology of schizophrenia as demonstrated by associations with childhood adversity (Egerton et al., 2016), maternal stress and immune activation models (Modinos et al., 2015). Therefore, this recent development in the dopamine hypothesis may lead to further research on interactions between these systems and better control of related variables in the future.

1.5.2 The Glutamate NMDA Receptor Hypofunction Theory of Schizophrenia

Olney et al. (1995, 1999), recognised that while antagonism at the dopamine D2 receptor was an effective treatment for the "positive" symptoms of psychosis, the persistence of symptoms in some individuals could not be accommodated by dopamine theories at the time. It was, however, known that NMDA receptor antagonists like the former anaesthetic phencyclidine (PCP) could induce psychosis (Luby et al., 1959). Also, that their preclinical studies with rodents had demonstrated neurons could be damaged by excessive glutamatergic transmission which might be consequent upon failures of inhibition. In particular, at the NMDA receptor where antagonism or other forms of NMDAR hypofunction could lead to the release of damaging quantities of glutamate and overstimulation at post-synaptic neurons. Also, depending on the duration and severity, this could promote reversible and irreversible morphological changes at post-synaptic neurons even neuronal death (Olney and Farber, 1995). It was further recognised this could be prevented by clozapine (also, the atypicals olanzapine and fluperlapine) and by many types of drugs which implicated different kinds of neurotransmitter receptors[11] where an important insight was that the major excitatory neurotransmitter glutamate regulates inhibitory tone "by tonically activating NMDA receptors on GABAergic, serotonergic and noradrenergic neurons" Olney et al., 1999, p.526. These, they proposed formed part of an NMDA network, however:

Conspicuously absent from the list of intrinsic components is the D2 dopamine receptor …. Does this signify that D2 receptors play no role in the NRHypo model? No, quite the contrary. We have found no evidence that D2 receptors function internally within the network, but we postulate that they may be exceedingly important extrinsic regulators of the network." (p.527)

[11] "NMDA Glu, nonNMDA Glu, m3-muscarinic, a2-adrenergic, GABAA, sigma and 5HT2A", Olney et al., 1999, p.526, i.e. incuding, muscarinic receptor antagonists, GABA-A "receptor facilitators", Sigma agents, Alpha2-adrenergic agonists (Olney and Farber, 1995).

It was further proposed dopamine may be involved in the release of glutamate but pathology might arise if dopamine resulted in too much inhibition. Twenty years on this awaits confirmation, however, as above, there is good evidence of striatal dysregulation. Also, Grace (2012, 2016) discussed further below, has demonstrated through preclinical studies that midbrain DA cells in the VTA may themselves be influenced by NMDAR hypofunction. (Also see Slifstein et al., 2015, above, on extrastriatal hypodopaminergia).

More recent support for a glutamatergic hypothesis comes from PCP and ketamine models of schizophrenia which induce NMDA receptor hypofunction, now widely regarded as being superior to those involving amphetamine challenge which increases synaptic dopamine availability (Kantrowitz and Javitt 2010). NMDA receptor antagonists can induce schizophrenia-like symptoms at low dose in healthy individuals, while exacerbating or prompting relapse in individuals diagnosed with schizophrenia (Newcomer et al., 1999, Coyle et al., 2012, Krystal et al., 1994). One PET study of chronic ketamine users revealed an upregulation of D1 receptor availability in the DLFPC, consistent with upregulations in animal studies after long-term dopamine depletion (Narendran et al., 2005). Moreover, Olney et al. (1995), proposed that NMDA receptor hypofunction might arise under other circumstances without recourse to a dopaminergic explanation as primary factor, for example, if GABAergic interneurons which bear them are missing (Benes et al., 1991).

1.5.3 GABA During Development and in the Mature brain

Many of the associations observed in schizophrenia appear to have a developmental aspect so part of the liability to schizophrenia may lie in the early foundations of the nervous system when, for example, electrical communication between cells via gap junctions is pervasive during embryonic development. In the neocortex, the patterns of oscillations "are thought to play important roles in wiring essential connections notably cortical maps and in other important functions including migration and proliferation" (section F in Ben-Ari et al. (2007). By the post-natal period oscillatory activity has given way to chemical communication in most neuronal populations although communication via gap junctions remains a feature of glial cells (Venance et al., 2000). Without the pruning of gap junctions, Hameroff (2010), has observed the entire brain could be "one uninterrupted synchronized syncytium." However, a sparser distribution enables a capacity for many "conversations" to arise through rhythms at different frequencies which may occur virtually simultaneously at different levels in local and more distributed networks.

An important neurotransmitter in the generation of oscillations is gamma-aminobutyric acid (GABA), (Whittington and Traub 2003; Traub et al., 2003) which serves many roles during early development as discussed in detail by Ben-Ari et al. (2007). These include an excitatory role, which following Hebbian principles, they suggest may enable neurons which fire together to also "wire together." Also, GABA receptors are active in the hippocampus, and possibly other areas, even before most synapses are functional. GABA's role as an inhibitory neurotransmitter, may be delayed until afferents to GABAergic interneurons have developed. Nonetheless, they observe, even at this stage there is a need to maintain a balance between GABA and the major excitatory neurotransmitter, glutamate, to avoid excitotoxicity.

Oscillatory activity remains an important feature in the mature brain where the synchronized activity of interneurons can induce synchronous activity in cortical neurons (Traub et al., 2001; Schmizt, 2001; Lytton and Sejnowski 1991) and is increasingly recognised as being relevant to schizophrenia (Hunt et al., 2017; Rowland et al., 2013; Sorman et al., 2011)[12] and the efficient function of working memory in healthy individuals (Yoon, Grandelis, and Maddock, 2016).

1.5.4 GABA Deficits in Schizophrenia

Widespread deficits in the GABA synthesising enzymes (glutamic acid decarboxylase) GAD 65 and 67 have been frequently observed in postmortem studies of schizophrenia (de Jonge et al., 2017). The isoform GAD 65 is concentrated around the synapses where its transcription is activity-dependent and so may be especially involved in dendrite to dendrite communication, whereas GAD 67, which is responsible for synthesising 80-90% of GABA is more widely distributed in the extracellular cytoplasm and believed to be involved in maintaining basal levels of GABA and therefore is a source of tonic inhibition. GABA is the major inhibitory neurotransmitter, capable of putting inhibition into excitatory glutamatergic circuits. While GABAergic interneurons also appear to be involved in the generation of oscillatory rhythms (section 1.5.5).

[12] It would appear the dopamine cells in the ventral tegmental area of the midbrain respond to a phasic signal (burst firing) from the pedunculopontine area, as described by Grace (2016) and can be entrained to produce a similar phasic signal: "Burst firing of DA neurons in the VTA is potently driven by glutamate from the pedunculopontine nucleus (PPTg) ….. acting on NMDA receptors." A proportion of these cells are already firing as a result of release from GABA-ergic inhibition (via a process that starts with increased activity in the hippocampus) which is necessary for transmission at the NMDA receptor, so it is wondered whether the burst firing confers a specificity to the signal that in some way is related to the "meaning" of the stimulus?

Oscillations in the gamma band (a broad range) are particularly suited to long-range communication and emerging evidence indicates these may prove highly important in supporting complex mental processes that require the integration of information across and within large scale networks. It is suggested here, on the basis of evidence from recent connectivity studies which indicated reduced connectivity in TRS individuals (Wang et al., 2015; Ganella et al., 2017, 2018) oscillatory behaviours may be especially relevant to TRS, although it is a matter for empirical research whether GAD deficits may be present in TRS and, if they are, whether they may be primary or secondary indicators of pathology. Similar questions apply to mitochondria which supply cellular energy and increase and decrease in number according to energy requirements, thereby supplying a marker of cellular metabolic activity and have been observed to be reduced in people with schizophrenia (PSZ) in the caudate and putamen (Somerville et al., 2011) and, distinctively, not in TRS (Roberts, 2017).

1.5.5 The Glutamate, GABA and Dopamine Neurotransmitter Systems Interact:

- Oligodendrocytes

There is now an extensive literature relating to myelin integrity, which may be vulnerable glutamatergic/ GABAergic dysfunction, for example, with observations of increased glutamate and increased lipid membrane metabolism coinciding in the frontal cortex and ACC of individuals with schizophrenia (Smesny et al., 2015). It has been observed "oligodendrocytes are highly vulnerable to glutamate" (Matute et al., 2006, p.215) and a lethal influx of calcium ions can follow brief agonism of the glutamate AMPA or kainate receptors expressed on oligodendrocytes. Moreover, excitatory activity at microglia can cause a damaging release of inflammatory cytokines, including tumour necrosis factor-α (TNF-α). The depletion of the antioxidant glutathione may also render cells vulnerable to oxidative damage (Matute et al., 2006). The particular vulnerability of oligodendrocytes to oxidative stress has also been commented upon by Vostrikov and Uranova, 2011 (p.6). The ways in which inflammatory, glutamatergic and oxidative processes may interact in schizophrenia are elaborated upon in a model advanced by Steullet et al. (2016), who propose an imbalance in one "hub" system (immune, glutamatergic, redox) can affect another.

In one postmortem study involving 7 PSZ and 7 age-matched control individuals, a 28% reduction in the number of oligodendrocytes in cortical layer 3 of the superior frontal gyrus, BA9 was observed. In addition, the spatial arrangements of the oligodendrocytes appeared

more dispersed (Hof et al., 2003). Similarly, Natalya Uranova has published a series of papers on schizophrenia reporting substantial reductions in oligodendrocytes: a 25% decrement in layer V1 and adjacent white matter of BA 9 (Uranova, et al. 2004); a 23% reduction in the number of pericapillary oligodendrocytes in prefrontal BA10 tissue (Vostrikov et al., 2008) and a decrease in the number of mitochondria in oligodendroglia in the caudate nucleus and BA10 along with signs of necrosis and apoptosis of oligodendrocytes in these areas (Uranova et al, 2001). With white matter decrements in schizophrenia potentially on such a scale it might be predicted these could reduce resting state connectivity (Koch et al., 2012), the conductance of axon potentials and perhaps even communication via oscillatory rhythms.

The diverse roles of other types of glia continue to be elucidated and extended, rising to a prominence and importance that may rival that of neurons. Bernstein et al. (2015), for example, observe that astrocytes "are now accepted as having crucial roles in brain functions, supplying neurons and oligodendrocytes (OLs) with substrates for energy metabolism, controlling extracellular water and electrolyte homeostasis, expressing neuromodulators, regulating neurotransmitter release, modulating immune responses." (p.6). Therefore, it is clear all these cell types, glia and neurons, are closely related and inter-dependent (Orthmann-Murphy, et al., 2008; Fields et al., 2015; Paolicelli et al., 2011). Interestingly, one aspect of clozapine's therapeutic efficacy might be an ability to protect against glutamate excitotoxicity or oxidative damage as demonstrated by Steiner et al. (2011) when the application of clozapine to immature oligodendrocytes (from the OLN-93 cell line) in vitro prevented excitotoxic damage that would have otherwise arisen in an energy-deprived medium (also see Ozcelik-Eroglu et al., 2014).[13]

- Synaptic Plasticity

Many theories have been generated during decades of schizophrenia research, however, separating out primary from secondary pathology is a major challenge, not least because neurotransmitter systems interact where they converge upon the same circuitry. Some examples, are provided below, including one concerning modifications in synaptic plasticity which may also readily translate to the idea of short-term memory as "activated LTM". It may be relevant to further note here that dopaminergic innervation of the DLPFC may be reduced in schizophrenia (Akil et al, 1999), however, understanding the effects of dopamine

[13] Relevant here might be the demonstration that clozapine can inhibit synaptic transmission at GABA A receptors by inhibiting post synaptic excitatory currents in isolated GABAergic neurons (Michel and Trudeau, 2000; also see Zink, 2004).

at D1 receptors is complicated by the inverted-U pattern of the post-synaptic response - where too little or too much stimulation can fail to produce an effect (Zahrt et al., 1997; Cools and D'Esposito, 2011; Colzato and Hommel, 2014). This pattern is not uncommon among neurotransmitters (Bentley et al., 2011) and so might provide a means, along with alterations in receptor density and neuromodulatory influences, of maintaining sensitivity (Vijayraghavan et al., 2007) and making fine adjustments as demonstrated below.

Dopamine neurons can modulate the excitability of glutamatergic cortical pyramidal neurons either directly at D1 receptors, or indirectly by synapsing upon GABAergic interneurons which bear D2 and D4 receptors where they may serve to stimulate GABAergic inhibition (Laruelle, 2014). Moreover, dopamine can act with exquisite precision in small populations at pre and post-synaptic circuits at glutamatergic synapses where receptors are not co-localised yet can co-operate to modify excitatory circuits through Hebbian plasticity, by creating a temporal window in which tonic GABAergic inhibition is lifted to enable synaptic transmission to occur.

Xu and Yao (2010) demonstrated this in layer V pyramidal neurons from PFC slices (prepared from C57BL/6J mice), where the inhibition was lifted presynaptically by dopamine acting at D2 receptors on GABAergic interneurons. In addition, the duration of the temporal window could be extended from 30ms by dopamine acting at D1 receptors postsynaptically. Timing is critical for spike timing–dependent long-term potentiation (t-LTP) to occur, "t-LTP is induced when presynaptic spiking precedes postsynaptic spiking within a narrow temporal window" (p.16366). A minimum 30ms period is required (Pawlak and Kerr 2008). Whether there are long-term alterations in synaptic plasticity, with possible related changes in long-term memory involving protein synthesis, may also be subject to other modulatory inputs from other neurotransmitters and neurohormones (Stephan et al., 2009).

- Parvalbumin-Containing GABAergic Interneurons

Deficits in GABAergic interneuron have been reported in post-mortem studies of schizophrenia (Benes et al., 1991) which could compromise the generation of gamma oscillations in recurrent micro-circuits and the related ability to synchronise different streams of information which is an important aspect of cognitive function (e.g. Lodge et al., 2009; Andersson et al., 2012; Lewis et al., 2012; Whittington and Traub, 2003). The integration and "binding" of information is hypothesised to arise through observable

synchronisation of oscillatory rhythms. Moreover, deficits in PVIs may lead to disinhibition of the pyramidal cells (Lewis and Gonzalez-Burgos, 2006; Lisman et al., 2008).

There is also a literature in schizophrenia on PVI deficits arising in context of maternal stress and maternal immune activation (Uchida et al., 2014, Canetta et al., 2016, respectively), also, through increased vulnerability to redox dysregulation in a model where vulnerability to oxidative stress (through reduced levels of antioxidant)[14] was increased with decrements arising early in postnatal development and during the equivalent of adolescence but not in older animals (Cabungcal et al., 2013a).

1.5.6 The many actions of Clozapine

"The failure of current science to explain the unique mechanism of action of clozapine is one of the most humbling aspects of the current situation." (Nutt & Need, 2014, p.1183)

Clozapine has a range of potentially beneficial therapeutic actions and so could benefit individuals in different ways and, perhaps, at different stages of the illness. Some support may come from the variation in time courses demonstrated in a prospective 1-year study by Fabrazzo et al. (2002) where some participants responded only towards the end of the trial. Despite its low liability for ESPE, clozapine does have affinity for D2 receptors (Seeman and Lee, 1975), however it is distinguished by fast on/ fast off binding, for possibly 12-24 hours, whereas some conventional antipsychotics may bind for days (Seeman, 2011).

Clozapine also has especially high affinity for the dopamine 4 (D4) receptor, described by Seeman (2011) as having a potency that is about 10 times than for D2 receptors. The D4 receptor is present at high density in some areas implicated in schizophrenia, for example, in the hippocampus and striatum (Brady et al., 2012, page 1005). Similarly, it is enriched in the anterior cingulate cortex (ACC) where a novel role has been proposed "in gating responses to reward-salient stimuli" (Cocker et al., 2016, p.191). mRNA analysis by De Almeida and Mengod (2010) revealed the D4 receptor is more densely represented than the D2 receptor in layer V of the monkey PFC where layer V has likely projections to the striatum. This differential expression in the PFC is summarised in Table 1. 2 and it is proposed here that one of the many potential reasons for clozapine's efficacy could lie in the high density of D4 neurons on parvalbumin containing interneurons (PVIs) which are

[14] i.e. redox dysregulation: " Oxidative and nitrosative stress result from an imbalance between overproduction of reactive oxygen species (ROS), and reactive nitrogen species (RNS) on one side and deficiency of enzymatic and nonenzymatic antioxidants on the other side" (Do et al, 2009, p.220)

vulnerable to damage from calcium influx due to slow kinetics, which, however, facilitate sustained activity in the prefrontal cortex (PFC), thereby prolonging depolarization and increasing synaptic summation, which brings a neuron closer to its threshold for spike-firing. This promotes synaptic plasticity and cognition (Cabungcal et al., 2013 (b); Steullet, 2016; Monaco et al., 2015).

Table 1. 2 Clozapine has high affinity for D4 receptors which are expressed at high density in the Prefrontal Cortex, Anterior Cingulate Cortex, Hippocampus and Striatum

Percentage of neurons in the prefrontal cortex expressing:	**D2 mRNA**	**D4 mRNA**
Glutamatergic Neurons*	52%	75%
GAD¬ + interneurons	34%	47%
Parvalbumin interneurons (chandelier morphology)	15-20% antipsychotics act here	65% clozapine may act here.
Calbindin interneurons (double bouquet morphology)	37%	37%
* These percentages imply some co-localisation of D2 and D4 receptors on glutamatergic neurons. ¬ Glutamic acid decarboxylase.		
After de Almeida and Mengod, (2010)		

Preclinical studies have shown clozapine increases dopamine in the prefrontal cortex and may restore dopamine turnover after chronic exposure to the NMDA receptor antagonist phencyclidine. Elsworth et al., 2008 (p.495) suggested this might be attributed to the role of clozapine as a selective D4 antagonist, which would be compatible with the proposal based on the obsevations of de Almeida and Mengod (2010) above.

Clozapine also has high affinity for serotonin receptors, especially of the 5-HT2 type. Farber (1998) presented evidence that clozapine has actions at the 5HT2A receptor proposing this may be a reason for clozapine's superior's efficacy as it exhibits strong binding affinity for the 5HT2A receptor where it acts as an antagonist.[15] It has been suggested that 5-HT2A antagonists may ameliorate negative symptoms and cognition in schizophrenia (Roth et al., 2004; Akhondzadeh et al., 2008 cited in Steeds et al., 2015). Interestingly, LSD is a serotoninergic agonist at several 5-HT2 subtypes and has been

[15] This is not unique to clozapine as chronic treatment with atypicals at clinically relevant doses, including clozapine, may antagonise 5HT-2A while stimulating 5HT-1A receptors (Meltzer and Massey, 2011). In the prefrontal network described by Sumiyoshi et al., 2013, both 5-HT1A and 5-HT2A receptors are depicted on a GABAergic interneuron (figure 7, p.5).

associated with psychosis.[16] NMDA receptor hypofunction was also proposed to affect serotonergic neurons (Olney et al., 1999). In a study of knock-out mice that lacked markers for the presynaptic serotonergic system, Yadav et al. (2011), observed the pre-synaptic serotonin system must be intact for clozapine to normalise NMDAR function.

As discussed at the end of the section 1.5.2, clozapine is very effective against NMDA receptor hypofunction induced excitotoxicity and prevents psychotomimetic symptoms (Farber et al., 1998). Clozapine and olanzapine were included in a list of agents by Olney et al. (1999, page 1001) with efficacy against NMDAR antagonism.[17] Farber et al. (1999) added glycine and D-cycloserine, indicating the latter might be more suitable. (p.13) D-cycloserine is a partial agonist at the glycine site on NMDARs, while glycine is a full agonist at the same receptor so both agents may promote glutamatergic transmission. Clozapine may achieve this by inhibiting system A-type glycine transporters (Javitt et al, 2004). It also appears to be an agonist at the glycine site (Moghaddam & Javitt, 2012, p.12).

Interestingly, clozapine at therapeutically relevant doses, may be capable of reversing hypermethylation associated with epigenetic changes (Guidotti and Grayson, 2013; Gillespie et al., 2017), as might be incurred in prenatal immune activation and prenatal stress models of schizophrenia. Gene expression of the GABAergic system in the adult prefrontal cortex and medial prefrontal cortex has been observed to be especially vulnerable in these models (Richetto et al., 2014, 2017; Matrisciano et al., 2013).

Taken together these observations suggest that clozapine's therapeutic actions may work on several levels, for example, it may improve both cognitive and negative symptoms through serotonergic actions, protect against neurotoxicity consequent upon NMDAR hypofunction or energetic failures, and it may, through its high affinity at the D4 receptor help to compensate for impaired dopamine transmission in the prefrontal cortex.

The origins of TRS may be neurodevelopmental, however, as Olney et al. (1999) proposed, pathology may only arise as circuitry matures. Recent evidence of a common

[16] Farber et al. (1998) observed LSD may effectively counter neurotoxicity caused by NMDAR antagonism: "Among the 5HT2A agonists examined and found to be neuroprotective are LSD and related hallucinogens. The apparent contradiction in proposing that these agents might have antipsychotic properties is resolved by evidence linking their hallucinogenic activity to agonist action at 5HT2C receptors, whereas antipsychotic activity would be attributable to agonist action at 5HT2A receptors", p.57.

[17] Clozapine and olanzapine are "an order of magnitude more effective" than conventional antipsychotics (Farber et al., 1998, p.58 cite their earlier studies)

endophenotype with unaffected siblings (as identified by Wang et al., 2015) suggests the emergence of TRS is not inevitable but perhaps may require further insults or conditions of vulnerability. Moreover, Wang et al., 2015 identified some patterns of connectivity which were not shared with healthy controls or TRS individuals, but were unique to the unaffected relative which, they proposed, might represent resilience.

The lack of sex difference in the incidence of TRS cases identified by Wimberley et al., 2016, may provide a further clue to the nature of TRS, as this is a marked difference from most studies of schizophrenia where there is a greater proportion of males at the younger end of the spectrum. This might suggest that TRS pathology becomes active before the potentially protective effects of female hormones are fully available, whether due to an earlier onset or perhaps because of maturational delays at the menarche. Sex hormones are also synthesised in the brain, and it has been observed for example, that ovarian hormones may help to limit damage from excitotoxicity following a stroke or delay the onset of neurological disorders like Parkinson's disease. A circumstantial argument might also be constructed for clozapine because it greatly upregulates the production of allopregnenolone, a metabolite of pregnenolone which has shown promise in the treatment of schizophrenia in randomised controlled trials (e.g. Marx et al., 2014; Kreinin et al., 2014; Ritsner et al., 2014). A large randomised control trial of estradiol for TRS has also been conducted in female participants, demonstrating dose response effects on the reduction of symptoms measured on the PANSS (Kulkarni et al., 2015).

It is concluded clozapine works on many levels and may benefit individuals in different ways. A better understanding of the nature of pathology, disease stage, interactions with ageing and other factors in the individual may lead to more personalised treatment and perhaps it may be possible to use adjunctives or move on from clozapine once stability has been restored.

1.5.7 A Reconciliation

Following the unexpected observations of Slifstein et al. (2015) concerning hypofunction of dopamine in extrastriatal areas in schizophrenia, Abi-Dargham (2017) proposed dopamine might modulate the excitability of gamma-aminobutyric acid-ergic (GABA-ergic) cells in the hippocampus "as it does in the cortex" and lead to a dysregulation of midbrain dopamine firing. In support, she referred to the work of Anthony Grace (2017), who has conducted extensive work on the methylazoxymethanol acetate (MAM) mouse developmental model

of schizophrenia[18]. Grace (2012, 2016) has proposed the hippocampus is the primary site of pathology in schizophrenia, possibly, several synapses up (via the ventral pallidum and nucleus accumbens) from dopamine cells in the ventral tegmental area (VTA) which are mostly kept under tonic inhibition. However, those active VTA cells will be capable of responding to glutamatergic transmission at their NMDA receptors since depolarisation removes a magnesium block in the ion channel. Grace (2012) observed the hippocampus, by determining the number of active dopamine neurons, can control the strength of the signal that is then sent to the striatum in response to a behaviourally relevant stimulus.

In addition, Abi-Dargham (2017) provided an "overarching model for a "dual hit" on DA function in schizophrenia": the first "hit" concerns dopamine-related genes which may bias developmental trajectories, as illustrated by another impressive model, the D2R-OE transgenic mouse model (Simpson and Kellendonk, 2017, 2010; Kellendonk et al., 2006). This has demonstrated how a transient over-expression of D2 receptors in the striatum late in embryonic development can also lead to the emergence of a schizophrenia-like phenotype with maturation around the mouse "adolescence". The second "hit" relates to environmental risk factors, e.g. "drugs, stress, urbanicity, diet, and inflammation." In both the MAM and D2R-OE models, the schizophrenia phenotype emerges during the adolescent period when Olney et al. (1999) proposed maturation of circuitry permitted the development of psychosis. Pertinent to the second "hit", Du and Grace (2016) were able to restore stress responses in their MAM model to resemble controls and avert damage to the hippocampus by administering diazepam for 10 days during the adolescent period. This also appeared to prevent the emergence of a psychosis-like phenotype as the adult rats did not exhibit hyperactive DA neuron firing, hyperactivity in the amygdala, increased anxiety behaviours or hyperlocomotion to amphetamine.

[18] Mitotoxin methylazoxymethanol acetate administered to a pregnant rat on gestational day 17 stimulates a maternal immune response, followed by a schizophrenia-like phenotype in offspring which emerges around puberty: with exaggerated responses to amphetamine and PCP; deficits in pre-pulse inhibition, latent inhibition and reversal learning and set shifting; atrophy and increased cell packing throughout the ventral hippocampus (analogous to the anterior hippocampus in humans) and medial prefrontal cortex. The number of spontaneously firing dopaminergic cells in the Ventral Tegmental Area (VTA) of the midbrain, approximately doubles.

1.5.8 Genetic Evidence

Schizophrenia is a highly heritable disease, for example, Wray and Gottesman (2012) derived a heritability estimate of .67 from their study of the Danish register, which is perhaps surprising because according to classical argument schizophrenia might be expected to be under negative selection pressure and disappear since a lower rate of reproduction is associated with this disorder. This does not appear to be the case so either de novo mutations in families are very common or the disorder involves polymorphisms which individually carry very little risk. Indeed, both arguments may apply. The most recent evidence emerging from GWAS studies that have merged databases supports the view that the origins of schizophrenia probably involve many genes of small effect. These have also supported the major theories relating to dopamine, glutamate and GABA referred to in this introduction, for example, an enrichment of genes has been observed concerning GABAergic transmission, glutamatergic signalling and synaptic proteins (particularly, NMDARs). Many had already concluded multiple genes were involved after years of non-significant genetic associations (Pocklington et al. 2015; Ohi et al., 2015).

However, while the results of the CRESTAR study on the genetics of TRS[19] are awaited Gillespie et al., 2017 identified a study by Joober et al., (2005) which indicated TRS may have a higher familial loading than non-TRS. Another study indicated first-degree relatives of TRS individuals had a higher risk of developing a schizophreniform disorder (Silverman et al., 1987).

Moreover, there is a growing list of studies involving unaffected first-degree relatives of individuals with schizophrenia which have been finding evidence of similarities which, while not pathological by themselves, may be indicative of a shared endophenotype. This has been proposed for the rare early onset schizophrenia (by the age of 12 years). Using morphometry analysis, Gogtay et al. (2012) observed slower white matter development trajectories, relative to healthy controls, in the left parietal lobes of unaffected siblings of individuals with early onset schizophrenia (EOS) between the ages of 7 and 14 years, however, this normalised by the age of 18 years. In an earlier study, grey matter growth trajectories, which followed an inverted-U pattern reflecting synaptic pruning after puberty, were also altered in unaffected siblings who exhibited early deficits in the PFC and temporal

[19] Research to identify pharmocogenomic biomarkers of TRS is currently being conducted at King's College, London led by Professor David Colllier (CRESTAR).

cortex but not in the parietal cortex, unlike their EOS siblings, which prompted a proposal that changes there might involve a non-genetic stimulus. The deficits were normalised in the unaffected siblings by the age of 20 years (Gogtay et al., 2010). While these studies do not address TRS, they do reveal developmental trajectories and raise the possibility of deficits in unaffected siblings which subsequently normalise with maturation.

Decrements have been observed in ACC volumes for first-degree relatives and those at high-risk (Ohi et al., 2017 (a), Fornito et al., 2009). Moreover, Wang et al. (2005) observed abnormal connectivity in the healthy siblings of TRS individuals. Further, in a review of 58 studies, cognitive deficits, were observed in unaffected siblings particularly affecting executive/ cognitive control and auditory verbal learning (Snitz et al., 2006); intellectual asymmetry favouring the verbal subscale over the performance subscale was reported in unaffected first-degree relatives of PSZ (Karvariti et al., 2006). Perceptual deficits have also been observed (Keri et al., 2005, 2004; Gracitelli et al., 2015, 2013). In addition, using fMRI, de Leeuw et al. (2015) observed reduced activation in the ventral striatum, supplementary motor area (SMA) and insula during reward anticipation relative to healthy controls. Further this correlated with negative symptoms. Finally, there is some limited evidence that there may be an increased predisposition towards hyperglycaemia in schizophrenia which is independent of medication. This may also apply to unaffected first-degree relatives who have also exhibited glucose dysregulation which might, perhaps, affect energy homeostasis and undermine cognitive function (Thakore et al., 2002; Fernandez-Egea et al., 2008; Henderson et al., 2005; Guest et al., 2011). However, it is difficult to separate genetic from shared environmental factors.

After major advances in the last couple of decades, genetic research has entered a new exciting phase where molecular and metabolic pathways associated with genes are being explored in great detail. Further, metabolic profiles can be generated and collated. However, Horvath et al. (2015) have cautioned “These are monumental tasks and they will many years to complete.” In the meantime, integrative and systems approaches may be used to converge upon the areas that might be most accessible to current methods.

1.6 Treatment Resistant Schizophrenia

Kapur (2003) proposed that antipsychotic treatments "do not erase the symptoms but provide the platform for a process of psychological resolution", but unfortunately this does not always happen. While positive symptoms usually abate, cognitive and negative symptoms may remain. A widely repeated observation is that around 30% of individuals with schizophrenia do not respond to treatment with conventional antipsychotics (Meltzer 1997; Nakajima et al., 2015; Mouchlianitis, McCutcheon, and Howes, 2016 (a). However, Kane et al. (1988) demonstrated clozapine brought symptomatic relief to a sizeable proportion of their "severely ill schizophrenic patients, previously considered by many to be beyond the reach of conventional therapy." This has been repeatedly observed since, so clozapine is frequently described as the "gold standard" for TRS (Meltzer, 2012). However, not everyone who may be eligible for a trial of clozapine will receive it and TRS is associated with residual symptoms and worse outcomes (Iasevoli et al., 2016). In addition, there are other individuals, perhaps 5-10% of all cases, who derive no benefit from antipsychotic medication (Pantelis and Barnes, 1996) and might be described as "clozapine-resistant", "treatment refractory" (Kelly et al., 2010), or "ultra-treatment resistant" (U-TRS), for whom polypharmacy is the remaining option although the evidence base appears weak[20] (Cipriani, Boso, and Barbui 2009; Wimberley et al., 2016).

Since the inception of this study, the evidence for TRS as distinctive aetiopathological subgroup has advanced in important ways, for example, an epidemiological study of 8044 individual with a diagnosis of schizophrenia in the Danish national register with the aim of identifying predictors of TRS has been published by Wimberley et al. (2016). As clozapine may be under-prescribed, two criteria were employed to identify TRS individuals: one based on the prescription of clozapine; also a broader proxy definition based on a hospital admission after two courses of monotherapy with different types of antipsychotic - modelled in so far as possible on the criteria proposed by Kane et al. (1988). Using this approach, 21% of 8044 individuals in this study fulfilled either criteria for TRS - confirming some earlier estimates (Kerwin and Bolonna 2005).

This is, of course, a sizeable subgroup within a disorder that affects millions of people worldwide. Wimberley et al. (2016) identified some biological differences from the main sample of those who did not show signs of treatment resistance, for example, the TRS group had an earlier age of onset and were more likely to have already been an inpatient when they

[20] In the epidemiological study of the Danish national registry by Wimberley et al. (2016), over a 10-year period, 44% individuals had received polypharmacy continuously for at least 90 days.

were diagnosed with schizophrenia[21]. The well-established risk factor of being male was also absent in the TRS group (one meta-analysis by Aleman et al. (2003) indicated an incidence risk ratio of 1.42). Urbanicity was associated with TRS, but in the opposite to direction to usually associated with schizophrenia (possibly indicating environmental stresses and toxins were less likely to be involved in the development of TRS). It is also interesting the TRS broader definition group (extending to those who were eligible for a trial of clozapine) did not differ from responsive individuals on the basis of family history, season of birth, early parental loss or paternal age. Just over half were living alone and around 30% were employed. The levels of long-term disability benefit were similar across the groups, around 14%. These latter figures, while perhaps reflecting aspects of Danish society, could indicate better functional outcomes for some than might have been expected.

Importantly, two longitudinal studies (Demjaha et al., 2017; Lally et al., 2016) have reported most cases of TRS are present at the point of FEP (usually defined as a first hospital admission or diagnosis relating to schizophrenia). Demjaha et al. (2017), reported treatment resistance was present from an early stage in 84% of those in their sample who were subsequently identified as having TRS. Their analysis also supported the observation made by Wimberley et al. (2016) of a younger age of onset (the mean age of the TRS at first diagnosis was 25.4 years compared to 30.1 years for responders). While Lally et al. (2016) concluded TRS was present from the outset in 70% of those who subsequently met the criteria for TRS in their sample. In the remaining 30%, symptoms had initially appeared to remit with first-line antipsychotics for a minimum of six months but failed to respond subsequently to another first line antipsychotic. They observed it has been estimated that 50% of TRS cases might arise from an upregulation of D2 receptors in response to pharmacological blockade leading to the development of supersensitivity to dopamine in the striatum (Chouinard and Chouinard 2008). The idea of "breakthrough" DA supersensitivity leading to a form of TRS is also given credence by Demjaha et al. (2012) and Seeman (2013). Consistent with Wimberley et al. (2016), both studies reported a prevalence of TRS in 23% of their samples.

The study by Demjaha et al. (2017) further revealed a higher level of negative symptoms and a longer duration of untreated psychosis independently predicted TRS. (The nature of negative symptoms and whether they are related to cognitive deficits in TRS will be further explored below). The question of whether the duration of untreated psychosis (DUP) might

[21] Researchers from the same team (Schneider et al., 2015), have noted the beneficial use of clozapine in childhood onset schizophrenia.

be related to outcomes and/or illness progression has been of great interest in the wider literature where findings have been mixed. In a prospective 10-year longitudinal by Barder et al. (2015), a subgroup exhibited a significant decline in scores on the working memory test of digit span, but this was associated with duration of psychosis after the start of treatment and not DUP in the prodrome. This group also had a lower IQ than the group with the shortest duration of psychosis after the start of treatment (a mean IQ of 96 compared with 105), thereby highlighting another potential vulnerability. In a systematic review, Rund (2014) identified only 6 studies out of 35 where there were significant correlations between DUP and changes in brain structure, however, this could not settle the question as to whether active psychosis might have the potential to be neurotoxic.

This is of particular concern in the case of TRS where there may be delays in accessing clozapine, and perhaps an increased risk of non-compliance issues with ineffective treatments. A concern shared by Harvey and Rosenthal (2016), who in their review of TRS refer to Boonstra et al. (2011), where the duration of untreated illness (DUP) preceding the first episode was unrelated to changes in brain volumes after 5 years, whereas the level of symptoms at baseline during the first episode were. This would be compatible with a hypothesis that symptoms in an attenuated form are not neurotoxic whereas the intensity associated with psychosis itself might be. In support, a longitudinal study over an average period of 7 years, reported decreases in whole and frontal brain volumes and reductions in white matter in the frontal and temporal lobes were associated with the duration of relapses (Andreasen et al., 2013). Moreover, in a study of 162 individuals medicated with clozapine, Ucok et al. (2015) reported a more favourable response to clozapine was likely if the duration of illness was shorter before the initiation of clozapine, the number of antipsychotic trials were fewer and individuals were younger.

Side-effects from inappropriate treatments could be a factor in deterioration, for example, one PET study with 6 TRS individuals receiving neuroleptic medication observed a blockade of 95% of D2 receptors in the striatum (Coppens et al., 1991). This helpfully excluded the possibility that a D2 blockade was not being achieved in these chronically unwell participants, but its extent would now be regarded as exceeding therapeutic limits.

However, as observed in the SPECT study of Abi-Dargham et al. (2000) above, striatal dopamine dysregulation may not be characteristic of all cases of schizophrenia. This has been reinforced by a seminal PET study by Demjaha et al. (2012) where TRS participants did not exhibit elevations in striatal dopamine synthesis capacity relative to healthy controls, unlike matched FLRS participants. While all the clinical participants were receiving

antipsychotic medication, none were taking clozapine and the TRS group exhibited a high level of symptoms (with total PANSS scores greater or equal to 75), whereas the FLRS group were described as having mild or absent symptoms on all PANSS items. Kim et al. (2017) subsequently addressed this imbalance by repeating the experimental design but also matching the TRS and FLRS groups with respect to symptom severity (presumably, this was now possible because the TRS participants were taking clozapine). Again, DA synthesis capacity was significantly lower in the TRS group relative to the FLRS group, across the whole striatum (and also the subdivisions), thereby affirming this important distinction and its potential as a biomarker of treatment responsiveness.

1.6.1 Considerations Concerning the use of Clozapine

In 2008, in the US, clozapine was used to treat just 4.4% of individuals with schizophrenia, indicating it is under-prescribed in some countries and not accessed by many who could benefit from it (Meltzer, 2012). The situation in England and Wales appears more reassuring as a recent audit of prescribing for 5,055 individuals with a diagnosis of schizophrenia, or schizoaffective disorder, revealed 23.7% were receiving clozapine, similar to the estimated prevalence of TRS by Wimberley et al. (2016). However, Patel et al. (2014) also identified cases of treatment resistance where in 8.5% where "no clear reason" was documented as to why a trial of clozapine had not been undertaken.

One consideration may involve the requirement of regular monitoring as clozapine requires titration to therapeutic levels as there is no direct relationship between oral dosage and the achievement of stable therapeutic levels of clozapine and its major metabolites in plasma. These are influenced by rates of metabolism in the liver, associated with allelic variation in the cytochrome P450 system (Aitchison et al., 2000). Moreover, smoking can speed up clozapine clearance considerably so care needs to be taken upon cessation as this could lead to excessive sedation or seizure (Maccall et al., 2009, Rostami- Hodjegan et al., 2004). Regular measurement of white blood cell counts is also required to identify developing agranulocytosis which is life-threatening (Kelly et al., 2007).

More common side-effects may also deter, for example hyper-salivation, a high risk of considerable weight gain, hyperglycaemia, dyslipidaemia, diabetes, hypertension and further problems which may be related to these, including myocarditis (Whitney, et al., 2014). In one study of 84 patients taking clozapine, 46.4% had metabolic syndrome and, possibly, only olanzapine rivals clozapine for this liability (Ahmed et al., 2008; Wu et al., 2008). However, such concerns are eclipsed by the considerable clinical benefit it can bring.

Clozapine also has the advantage of a very low liability for distressing and potentially irreversible extra pyramidal side effects (EPSE) such as involuntary "pill-rolling" movements of the fingers, dyskinesias and distorted movements of the tongue and mouth. For research and clinical purposes, it is also important to note that unlike other antipsychotics, it may take some considerable time to produce a therapeutic effect: in a one-year prospective study of the response to clozapine at a fixed dose with TRS individuals who, apart from one, met the Kane criteria for TRS, some individuals converted to a clinical a response at six months and, impressively, 71.8% of the 32 participants had responded by 12 months (Fabrazzo et al., 2002).

1.6.2 A Challenge to Clozapine's Superior Efficacy

Clozapine's primacy as the "gold standard" in the treatment of TRS and for reducing suicidal behaviour (Meltzer, 2012), has recently been questioned as a result of a meta-analysis conducted by Samara et al. (2016), who observed the evidence base involves comparisons with first-generation antipsychotics. Also, that the large effect size of the original study (Kane et al., 1988) has never been replicated while more recently a Cochrane review involving simple pair-wise comparisons with "atypical" antipsychotics did not find clozapine to be superior (Asenjo Lobos et al., 2010). Their own meta-analysis of 40 single or double-blind randomised control trials involving more than 5,000 participants, with changes in symptom levels as the main outcome measure, revealed a surprising result: clozapine was not significantly better than most other drugs, atypical and typical, including olanzapine and risperidone.

One possible explanation advanced by Samara et al. (2016), is the extra contact with services required for clozapine may introduce a form of bias when research is not blinded and it is further observed here, by the time a patient considers clozapine they may be more reconciled with their condition, more compliant and accepting of the need for treatment. However, as Samara et al. (2016) acknowledged it is difficult to blind research involving clozapine because of monitoring protocols; also, they had excluded three large non-blinded studies which supported clozapine's superiority. Taylor (2017) described the first trial conducted by Kane as "perhaps one of the last truly blind studies of clozapine" as staff and investigators were unfamiliar with it. Kane and Correll (2016) writing in the editorial of the issue where the meta-analysis appears, further noted patients who are severely ill are less likely to enrol in demanding and complex randomised control studies; also the identification of TRS may be less stringent than in earlier studies. Moreover, individuals may be less responsive to clozapine if it is introduced at a later stage of illness (Nielsen, Nielsen, and

Correll, 2012; Ucok et al. 2015) and some of the subgroup and post hoc sensitivity analyses conducted by Samara et al. (2016) had low statistical power.

The meta-analysis was "unarguably well conducted" (Taylor, 2017) and revealed differences in dosage across studies which were described by Kane and Correll (2016) as "potentially very important" because, as discussed above, clozapine is the only antipsychotic where an association has been reliably observed between drug plasma levels and the clinical response: the meta-analysis revealed a mean dose of 392 mg/d had been administered in the studies involving comparisons with the atypicals - well below the average of 511 mg/d in the earlier studies using first generation antipsychotics. Recognising this as an issue, Samara et al. (2016) comment "the likely underdosing in industry-funded trials could constitute a serious problem that could have affected the results." (p.207)

Kane and Correll (2016) agreed more research is needed, but some comfort might be taken from a study by Agid et al. (2011) who applied an algorithm to trials that involved switching treatment between the chemically different[22] antipsychotics risperidone or olanzapine if there was no clinical response to the first; and then switching to clozapine if there was no response to either of these. They reported that 74.5% of 244 participants responded to treatment after 12 weeks, and among the non-responders who were switched to the other drug, 16.6% responded. However, among the treatment resistant individuals who then agreed to try clozapine, the response rate rose again to 75%. A further striking example of clozapine's efficacy, was observed by Rodriguez et al. (1997), discussed further below, where there was marked improvement in 17/39 participants who had been severely unwell and for approximately two decades.

[22] Risperidone and Olanzapine are both "atypicals" in that they have a higher affinity for 5-HT2A serotonin receptors than D2 dopamine receptors and thereby minimise the risk of EPSE. Olanzapine a selective monoaminergic antagonist with high affinity binding to Serotonin 5-HT, Dopamine, muscarinic, H1 and alpha receptors so perhaps it is here some efficacy lies). (Incepta Pharmaceuticals).

The pharmacological profiles of Olanzapine and Risperidone are quite different; for example, Olanzapine exerts strong antagonism at the muscarinic acetylcholine M2 and M3 receptors, while Risperidone does not (Lavalaye et al., 2001). Risperidone also has the interesting property of being a "qualitative" atypical because at lower doses it has greater serotonin antagonism than dopamine antagonism and so minimises the risk of EPSE.

1.6.3 The Need for the Consistent use of a Consensus Definition

One of the observations to emerge from the debate around the meta-analysis, is that judgements determining TRS are inadequate if based on clinical judgement alone. The terms "poor outcome schizophrenia", "deficit schizophrenia", "ultra-high resistant schizophrenia" and "Kraepelinian" schizophrenia" are all used in the literature but apart from those studies which state they have followed the Kane criteria, or a "modified" version, it is not always clear whether individuals have been given adequate trials of at least two antipsychotics and met other criteria for TRS or, alternatively, might be clozapine-resistant. This problem had been described two decades earlier by Conley and Buchanan (1997) who commented studies of TRS "have long been hampered by a lack of consistency in definition."

A working group on diagnostic guidelines and terminology for application in drug trials, led by Oliver Howes and including John Kane, was published in March 2017 (Howes et al., 2017). It presented the results of a systematic review of 42 randomized antipsychotic trials relating to TRS. This revealed that half did not provide details of operationalized criteria and in the remaining 21 studies, the criteria varied considerably to the extent that they were identical only in 2 instances. New guidelines have been presented for defining and reporting treatment resistance, what determines adequate treatment and represents treatment response: "Three key elements define the concept of treatment resistant schizophrenia: 1) a confirmed diagnosis of schizophrenia based on validated criteria, 2) adequate pharmacological treatment, and 3) persistence of significant symptoms despite adequate treatment." (p.217) These principles distil the essence of criteria used by Kane et al. (1988)[23].

TRS may also have been under-researched because it is prone to confounds relating to chronicity, age, co-morbidities and concerns about the effects of exposure to other antipsychotics and treatments. Associations between antipsychotics and structural changes have since been confirmed through regression in meta-analyses (Radua et al., 2012; Fusar-Poli et al., 2013). Interestingly, 7 years after a first episode, those individuals who had

[23] In this seminal study, TRS was defined using historical, cross-sectional (actual) and prospective outcomes: no good period of function in the previous 5 years; at least three treatments of different antipsychotics from at least two chemically different classes, at doses equivalent of 1000mg chlorpromazine for a minimum of 6 weeks; a high severity of symptoms (greater than 44 on the British Psychiatric Rating Scale), including two of the following: unusual thought content, conceptual disorganisation, hallucinatory behaviour, suspiciousness. That there should be no improvement, defined by a 20% reduction in symptoms after 6 weeks on haloperidol.

discontinued antipsychotic medication had double the recovery rate compared with those who had continued "maintenance" treatment (Wunderink et al., 2013). This is just one study but adds to concerns about antipsychotic treatment, but as discussed above, relapse may be neurotoxic (quite apart from other ramifications), and this is the clinician's "troublesome dilemma" (Andreasen et al., 2013). If the general effect of antipsychotics is to lower glutamate transmission (Egerton et al., 2017) and further downregulation in glutamatergic transmission occurs during the disease process, or with age, perhaps timing and duration is important.

On the evidence above, it is now clear TRS represents a sizeable subgroup who need a distinctive treatment strategy unless they are to run the risk of side-effects with ineffective treatments. A further implication is that disregard for the distinction between FLRS and TRS may have led to a potentially important confound pervading the literature, affecting well-conceived and carefully conducted studies especially those involving small groups, as might be found in pathology and molecular biology studies, contributing to mixed results, perhaps, for example, Beasley et al. (2001, 2002). There could also be an over-representation of TRS among altruistic donors because of a higher suicide rate and disease severity.

1.7 Brain alterations in TRS

1.7.1 Brain morphology in TRS

Even though few studies have been conducted with participants who meet the consensus guidelines definition of TRS, an extensive systematic review has been conducted by Mouchlianitis et al., 2016 (b) which identified 11 structural MRI studies that compared TRS individuals with healthy controls. In four of these, grey matter deficits were identified in at least 25 areas. The most commonly implicated areas being the left middle frontal gyrus, right middle temporal gyrus and right precentral gyrus.

Extensive reductions in GM were observed in TRS relative to FLRS groups by Anderson et al. 2015 (a), in the "superior, middle, and inferior temporal gyri, pre- and post-central gyri, middle and superior frontal gyri, right supramarginal gyrus, and right lateral occipital cortex". The U-TRS group showed reduced GM compared with FLRS in the right parietal operculum and left cerebellum. However, no differences were observed between the TRS group and ultra-TRS groups. This might possibly suggest that TRS and U-TRS are on a continuum, where in the latter the disease is too advanced to be helped by clozapine (a possibility which might also be inferred in Rodriguez et al., 1997 at 1.7.3).

Replicated reductions were observed by Mouchlianitis et al., 2016 (b) in the volume of the caudate nucleus consequent upon clozapine treatment, although it is suggested here this could reflect a reversal of the effects of treatment with conventional antipsychotics which have been observed to cause enlargement in this area. Progressive reductions in striatal volume might arise in "poor outcome" individuals (Mitelman et al., 2009; Li et al. 2018).

In a further systematic review (Nakajima et al., 2015) several studies were identified where structural predictors of the TRS had been reported. However, they were unaware of any prospective studies involving structural changes following treatment with clozapine. However, this review may have been conducted before Ahmed et al. (2015) reported progressive reductions in grey matter during the first 6-9 months after commencing clozapine. It was inferred grey matter loss might not necessarily be pathological as symptoms remitted and could, perhaps, reflect the pruning of aberrant connections. In addition, lesser decrements in the left medial prefrontal and right middle temporal cortices were associated with a greater likelihood of treatment response.

Looking beyond TRS, alterations have been observed in the gross anatomy of the orbitofrontal cortex in "deficit schizophrenia" which might include some TRS individuals. This is characterised by abnormalities in the patterns of sulci and gyri (Takahashi et al., 2017). A consortium meta-analysis led by Walton (2017) of PSZ, observed a correlation between negative symptoms and reductions in cortical thickness in the left medial orbitofrontal cortex which is implicated in an extensive network, including the thalamus, amygdala and ventral striatum relating to reward, identified by Menon (2011) as part of the Salience Network which includes the fronto-insular cortex and dorsal anterior cingulate as major nodes and may be influenced by the HPA-axis (Porcelli, Lewis, and Delgado 2012).

Palaniyappan et al. (2011), observed areal contraction of the surface area in schizophrenia in regions associated with the three major networks, as described by Menon (2011): the DMN, Central Executive and Salience Networks (especially in the left hemisphere). Residual negative symptoms in their clinically stable participants correlated with the degree of contraction in the DMN and SN, but not in the CEN. Also see Palaniyappan et al. (2013, a). These studies did not identify a TRS subgroup but TRS individuals may have contributed to these observations.

1.7.2 Brain function in TRS - A Dearth of Functional Neuroimaging Studies

Advances in computer power and the understanding of neural architecture, has also enabled the ongoing development and testing connectionist models of neural function that have been under way for around 40 years. More recently, fMRI has been used to distinguish between evoked and spontaneous intrinsic activity in the brain (Lu et al., 2007). Commenting on this distinction, Raichle (2009) observed a paradigm shift could be under way. Importantly, "the conclusion of several perspectives, is that the fMRI BOLD signal is best correlated with local field potentials" around pre and post-synaptic terminals. Moreover, those falling in the gamma band frequency (24- 80+) and those exhibiting much slower frequencies (described as slow cortical potentials (SCPs), including the delta band (1-4 Hz) bear the greatest similarity to those of intrinsic activity. Raichle proposed the correlation between the BOLD signal and SCPs, thereby provides a "bridge to highly relevant, rich and diverse neurophysiologic literature." (p.12732) This is also considered here to be highly relevant to understanding the anatomy of working memory in schizophrenia.

Since the inception of this project, the systematic review by Nakajima et al. (2015) on neuroimaging studies involving TRS has been timely. Using search criteria that include the definition of TRS as involving "a failure to respond to at least two antipsychotic medications" (p.171), they identified 25 articles suitable for review, however, only 3 used fMRI and only 5 directly compared TRS and non-TRS, nor did they find any replication of results. Another valuable systematic review of TRS, and related terms, conducted by Mouchlianitis et al., 2016 (b), above, involved a different database. Five functional MRI studies were identified (three resting-state MRI studies). Another used arterial spin labelling "in individuals with resistant auditory hallucinations showed increased cerebral blood flow in areas involved in speech processing" (p.452)[24]. The fifth was a small fMRI BOLD study by Fitzgerald et al., 2007 concerning 3 participants described as having treatment resistant auditory verbal hallucinations.

The diversity of the studies was commented upon which may be one reason this extensive analysis found few findings that had been replicated. Contrasting changes in the caudate were interesting as this might reflect dysregulation in the AST which might be expected differ between TRS and FLRS in the light of the observations concerning normal presynaptic synthesis of dopamine in TRS (Demjaha et al, 2012 and Kim et al, 2017), however as Mouchlianitis et al., 2016 (b) observed volumetric changes may be attributed to clozapine and atypicals having contrasting effects, which may be further complicated by sex

[24] Wolf et al. (2012) cited in Mouchlianitis et al., 2016(b). Also see McGuire et al., 1993.

differences (Scheepers et al., 2001; Heitmiller et al., 2004). The observation with the greatest replication was that of "a greater reduction in grey matter in resistant patients, predominantly in frontal areas." (p.458) This was a main finding of the impressive study by Anderson et al., (2015,a) who compared TRS with FLRS, clozapine non-responders (or U-TRS) and a healthy control group, however, evidence of replication was still modest.

There is perhaps, at least one fMRI BOLD study that may have escaped the searches in the above reviews, as it was not specifically concerned with treatment resistance or related terms, but which may be relevant to the research reported here: a cross-sectional n-back study conducted by Jansma et al. (2004) where 8/10 clinical participants were receiving treatment with clozapine. However, both reviews did identify one peer-reviewed fMRI BOLD study. This involved 3 participants meeting the TRS definition and 4 healthy control participants (Fitzgerald et al., 2007). Apart from the very small size of the sample, it should be noted that one of the participants was not receiving clozapine at the time. Mixing participants who are taking, or not taking, clozapine seems less than ideal.

This raises another important aspect of TRS research, which is the possibility that, in responders, treatment with clozapine may go some way towards "normalising" aspects of function. This highlights the value of prospective studies in this area and might also help to reconcile mixed observations. Also, while Fitzgerald et al. (2007), had a prospective design, the independent variable was treatment with rTMS. However, in retrospect, it did identify areas of differential contrasts with healthy controls which may be relevant to TRS - if not the direction, and that might not, in any case, reliably translate across methodologies or the stage of illness of participants. Fitzgerald et al. (2007), notably reported relative hypoactvation in the TRS group before treatment in the medial frontal cortex, extending to the inferior frontal cortex, anterior cingulate, left superior frontal gyrus and parietal areas. Greater activation in the left caudate and precentral gyrus was also observed.

1.7.3 Evidence Concerning TRS from Molecular Neuroimaging

Similarly, in one of the rare PET studies of TRS individuals who had responded to six months of clozapine treatment compared with conventional antipsychotic treatment for six months, Molina et al. (2007) observed "clear hypofrontality". An earlier study by Molina using single proton emission computed tomography (SPECT) compared participants after 6 months' treatment with conventional antipsychotics with a subsequent 6-month course of clozapine (Rodriguez et al., 1997; 1998). The possibility of hypofrontality had been indicated by reference to a normative database but not confirmed. However, comparisons

between the treatment groups indicated the non-responders to clozapine (which might be equated with ultra-treatment resistance) generally exhibited less perfusion with significant differences with the clozapine responders in the left inferior dorsolateral prefrontal cortex, right superior dorsolateral prefrontal cortex, thalamus and basal ganglia – resembling part of the thalamo-cortical loop circuitry. It is tentatively suggested here the lack of response might possibly reflect the endpoint of a more severe form of illness where structural deficits may have met their limits, (for example, through widespread dendritic atrophy).

Interestingly, a therapeutic response to clozapine was associated with a significant lowering of perfusion values in within-subject comparisons with conventional antipsychotic treatment in the basal ganglia bilaterally, thalamus and right superior dorsolateral prefrontal cortex and the left anterior prefrontal cortex. A further lowering of perfusion in the context of a therapeutic response seems counter-intuitive unless, perhaps, further brain changes occur in that time. This is quite possible since, as mentioned above (p.68), grey matter loss was observed by Ahmed et al. (2015), 6-9 months after treatment with clozapine had begun. Irrespective of the response, this was marked in the medial prefrontal cortex and also the periventricular area which is presumed to reflect atrophy in overlying structures (and so might include the basal ganglia).

The early SPECT study is important in several respects: firstly, for its rarity value and the relatively large number of participants (39 "treatment-refractory"), also selection of the clinical participants used criteria similar to Kane et al. (1988) and they defined the treatment response as being a 50% decrease on clinical rating scales for positive and negative symptoms. It was designed to look at the clinical response to clozapine after medication was switched from conventional neuroleptics with the differences between responders and non-responders providing outcome measures. Treatment with clozapine had the effect of lowering metabolism in responders to clozapine while, as indicated above, hypometabolism in TRS was affirmed in the prospective study by Molina et al. (2007).

Molina et al. (2007) also referred to research which demonstrates clozapine can raise concentrations of extracellular dopamine in the prefrontal cortex (Yamamoto, Pehek, and Meltzer, 1994; Moghaddam and Bunney, 1990). The overall effect of this may be to increase GABA release, thereby providing inhibition into this area: "this GABA release being coherent with a lower metabolic rate." (p.60) In support, they referred to a preclinical study by Grobin and Deutch (1998) that demonstrated dopamine can regulate levels of GABA in the prefrontal cortex, possibly through the actions of D2 agonism on interneurons. Laruelle (2005; 2014) has also highlighted the interaction between glutamatergic and

dopaminergic pathways and the potential consequences of a dopamine imbalance (between D1 and D2 receptors) upon NMDA glutamate receptor mediated function.

A study by Abi-Dargham et al. (2012) replicated and extended the observations of an earlier study that dopamine 1 (D1) receptors were increased in medication naïve individuals in the DLPFC, orbito-frontal cortex (OFC) and medial prefrontal cortex (mPFC) and normalised through antipsychotic treatment - the inference being that an ineffective upregulation occurs because of a loss of sensitivity to dopamine (Abi-Dargham et al., 2002; Rao et al., 2018). The 2012 study also demonstrated that prior exposure to anti-psychotics may have reversed this in a separate group of individuals who were drug-free at the time of scanning.

More recently, ACC hyperactivity has been observed in individuals who meet the Kane criteria for TRS, or a modified version, using proton magnetic resonance spectroscopy (Egerton et al., 2012; Demjaha et al., 2014; Mouchlianitis et al., 2016 (a) but not in participants who are being medicated with clozapine, raising the possibility that treatment may have normalised glutamatergic function although causality cannot be inferred given the cross-sectional nature of the studies (Goldstein et al., 2015). Moreover, it is important to emphasise, even if this were the case, the haemodynamic response to executive tasks in fMRI studies, may still be influenced to the by individual differences with respect to "the inverted-U" of sensitivity to dopamine which helps to inhibit or modulate glutamatergic transmission.

1.7.4 Evidence Concerning TRS from Connectivity Studies

At the point of writing, only three resting state connectivity studies exploring whole brain connectivity appear to have been published concerning TRS (Ganella et al., 2017, 2018; Wang et al., 2015), however, the preliminary impression is this approach may yield valuable biomarkers that may help diagnose TRS an early stage if, for example, TRS is well-characterised as a disorder principally affecting connector hubs in large-scale networks. The study by Ganella et al. (2017) explored and compared whole-brain functional connectivity in TRS participants who were taking clozapine with healthy controls. This involved 70 nodal pairings but the efficiency of a network is "inversely related to the number of intermediate regions that must be traversed for a pair of brain regions to communicate with each other." (p.74)

Possibly the most important observations concern a potential biomarker of TRS in the highly significant observations of reduced global efficiency along with increased local

efficiency in TRS participants relative to controls. Ganella et al. (2017) posed the important question as to:
"whether the findings in our study of TRS provide evidence to a unique pattern of connectivity in comparison to the extant literature in schizophrenia." (p.76)

It was further observed the mean duration of illness in the TRS group was 17.9 years and no relationship was found with global network properties. However, the authors commented this could reflect a ceiling effect on connectivity and perhaps also medication effects. Specifically, Ganella et al. (2017) observed reductions in connectivity strength in 228 functional connections (3.4%), while none of the regional pairings in the TRS group exhibited increases in connectivity strength relative to the control group. It was further established these reductions occurred across all six brain lobes[25], but were concentrated in the frontal, occipital and temporal lobes (also see Palaniyappan et al., 2013 (b), p.1813). The majority of reductions occurred between the frontal lobe and cuneus in the occipital lobe and between the occipital lobe and the paracentral lobule; also, between the fusiform gyrus in the temporal lobe and the occipital lobe, further, between Heschl's gyrus in the temporal lobe and the frontal lobe. There were some lesser decrements involving the parietal lobe and connections with the occipital and temporal lobes which were not commented upon. This might suggest these connections are relatively unaffected, alternatively, parietal connections are so important they are highly protected or maintained, for example, it has been proposed the posterior cingulate cortex (PCC) may have a role in the fine-tuning of the connectivity of intrinsic networks in the service of attentional focus (Leech et al., 2011; Leech and Sharp, 2014).

Further, the strong implication of areas involved in audition and visual perception lends strength to proposals made elsewhere in this thesis that TRS individuals may have early sensory processing deficits which may adversely impact upon the efficiency of encoding, short term learning of auditorily presented verbal material and executive task performance.

Interestingly, in the study by Wang et al. (2015) a group of unaffected siblings appeared to have some potentially compensatory connections which were increased relative to controls, but "moderately reduced" in the TRS group. These were "widespread, especially between the occipital and frontal lobes and between the parietal and temporal lobes." (p.101)

[25] Occipital, Temporal, Parietal, Frontal, Subcortical and Posterior.

Observations on the connectivity between the occipital and frontal lobes were supported when Ganella et al. (2018) expanded their earlier study to include rs connectivity measurements with unaffected siblings. It was observed brain networks exhibited increased local efficiency in both unaffected siblings and TRS compared with the control group. This confers greater resilience with respect to local network disruption and was present in all areas when the network was decomposed into four modules (i.e. distinct brain areas) but was significant only for the visual and cerebellar modules but not for the salience or default modules. It was further observed there were significant reductions in global efficiency for both groups relative to the control group, while there were no significant differences between the TRS and sibling groups.

1.8 Multiple Risk Factors and Integrative Approaches

Just as many scientists have broadened their perspectives on schizophrenia there has been an acceleration in research. This progress is reflected in Figure 1. 1 based on simple search terms applied to the Public Medicine database of the National Institute of Mental Health (U.S). This revealed more than 125,000 peer reviewed articles have been published on "schizophrenia" and in 2017 the number of articles was 6495, while 148 papers were published on "treatment resistant schizophrenia."

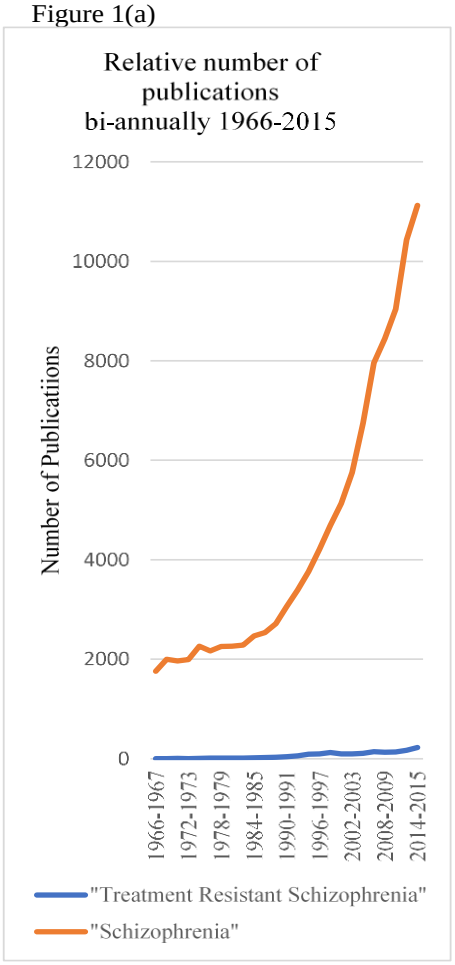
Many genes of small effect have been implicated in the pathogenesis of schizophrenia, along with a range of environmental and psychosocial influences which may be risk factors or precipitants of psychosis. As mentioned in section 1.1, these include poverty, urbanisation, migration, industrialisation and a loss of social support; also, exposure to toxins, disease, vitamin D deficiency, poverty and drugs of abuse. All of which might also have perinatal effects. An impressive accumulation of knowledge indicates various paths might lead to schizophrenia, impacting different individuals in different ways, contributing to the heterogeneity of the condition.

A useful way of organising and understanding the accumulation of knowledge has been achieved in integrative and bio-social models, e.g. Keshavan (1999, 2011), Maynard et al. (2001), Howes and Kapur (2009), Howes and Murray (2014), Murray et al. (2017), Abi-Dargham (2017). By accommodating the timing of insults and different pathological pathways, all these examples go beyond a simple, but effective, "multiple hits" approach.

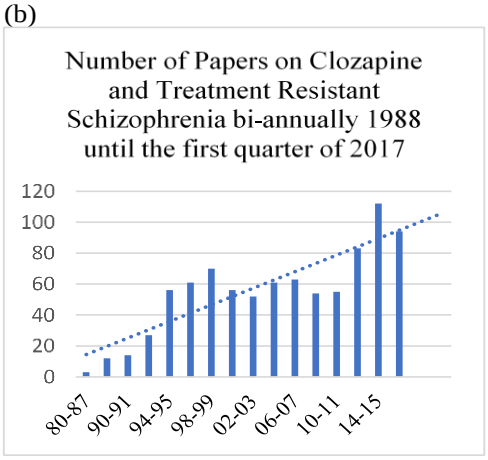
Figure 1. 1 Exponential Growth in Publications on Schizophrenia since 1966

Compared with those referencing Clozapine (b) and Treatment Resistant Schizophrenia (c).

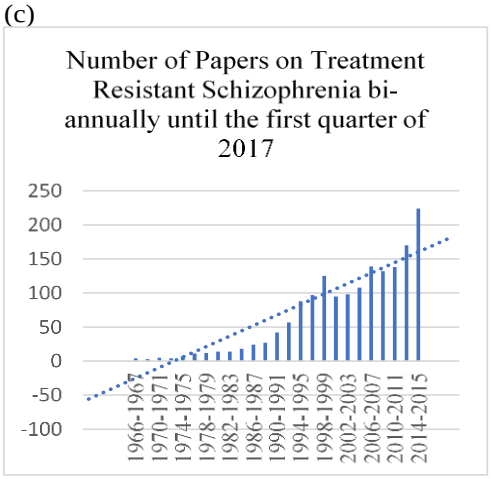
Figure 1(a)



(b)



(c)



Source: NIMH PubMed Database

where the burden of pathology overwhelms the processes of adaptation and repair. One of the achievements of an integrative approach is that has helped a range of seemingly disparate and odd associations with schizophrenia, such as season of birth, cannabis use and neurological “soft signs”, to be reconciled with the realisation that schizophrenia may, perhaps, be best characterised as a “developmental risk factor model of psychosis” (Murray et al., 2017) instead of the neurodegenerative theories which have prevailed historically.

One highly detailed and impressive contribution has been Keshavan’s (1999) ‘three hit’ model, which reconciled genetic and environmental factors with a glutamatergic explanation of pathology occurring during early and late development with possible neurodegenerative changes. A brain state was proposed where there was a reduction in tonic glutamatergic transmission consequent upon early neuronal loss and a subsequent pathological excess of

phasic activity after illness onset. It was also noted dopaminergic activity in the striatum is under the control of glutamatergic neurons, so dysregulation might predispose to hyper- and hypo-dopaminergia. More recently, Grace (2012, 2016), has described how tonic glutamatergic activity sets the responsivity of dopamine neurons in the ventral tegmental area (VTA) to phasic glutamatergic signals.

Further, Keshavan (1999) described periods of sensitivity across the lifespan when pathological factors might be especially potent as "windows of vulnerability." The first window concerned the perinatal period, for example, Keshavan highlighted the importance of glutamatergic transmission to neuronal migration. In the years since, evidence has accrued to suggest the fetus during the second or third trimesters may be vulnerable maternal stress (Yehuda et al. 2005), infection, malnutrition or intoxication which may degrade or overwhelm defences, including the placental barrier enzyme, 11beta-hydroxysteroid dehydrogenase. There may also be long-lasting effects on immune and endocrine function which continue into adulthood and may be reflected in associations with weight, blood pressure, stress reactivity, behaviour and brain alterations (reviewed by Reynolds, 2012). Moreover, associations between schizophrenia with the season of birth might be interpreted from an endocrine or immune perspective concerning the availability of food or increased risk of maternal infection during the winter (Bullmore, 2018).

Other risk factors include obstetric complications such as hypoxia during delivery, being born preterm and treatments associated with this; for example, the potentially life-saving administration of glucocorticoids (for example, to aid fetal lung maturation) may incur oxidative damage (Camm et al., 2011), while, a preclinical study by Virdee et al. (2016) found that antenatal exposure to dexamethasone "dramatically" increased mesencephalic dopamine neurons in the offspring, while, in a possible compensatory response, D1 receptors were downregulated in the adult ACC, prelimbic areas and striatum.

Keshavan proposed adolescence was a second window when a major reorganisation and pruning of synapses occurs (Keshavan 1999; Keshavan, Anderson, and Pettergrew 1994; Feinberg, 1982) along with unique "psychosocial stresses." There might be an association with immune regulation as microglia have a role in synaptic pruning (Paolicelli, et al., 2011; Perry and Teeling, 2013) where, for example, around 40-50% of excitatory synapses are lost in the DLPFC alone (Gonzalez-Burgos, et al., 2008). Around this time, as learning capabilities mature, for example, Monaco et al. (2015), citing Dumas (2005), observed that many NR2B subunits in NMDA receptors are switched from the NR2B to the NR2A form, thereby changing the slow kinetics on the post-synaptic spine which enable sustained firing

and support working memory. However, this also reduces the risk of excessive and damaging influxes of calcium ions. (This trade-off is described as a "double edged sword").

A third "window" related to disease progression with neurodegenerative changes observed in some individuals (Theberge et al., 2007; Aoyama et al., 2011) which might cause or exacerbate cognitive deficits. In view of sex differences in epidemiology (discussed above), parturition and the menopause could represent further windows of vulnerability, when the neuroprotection of ovarian hormones and neurotropins such as BDNF may also decline - e.g. Pluchino et al., 2009; Komulainen et al., 2008.

Integrative approaches such as that of Keshavan (1999) have apparent "face validity" by recognising schizophrenia is a complex and multifactorial disorder, involving interactions across different systems. Each re-articulation of major integrative theories reflects that so much more has been learned. This will continue as the "common language" of neurotransmitters, hormones and immune factors is decoded and more is learned regarding communication at the level of the networks - between local and global and through the various frequencies of oscillatory rhythms.

An example of the inter-relatedness of biological functions was provided by Brattsand and Linden (1996) when describing the interplay of the immune system and the HPA-axis:

Glucocorticoids inhibit the expression and action of most cytokines. This is part of the in vivo feed-back system between inflammation-derived cytokines and CNS-adrenal produced corticosteroids with the probable physiological relevance to balance parts of the host defence and anti-inflammatory systems of the body. (p.81)

Moreover, it is apparent, NMDA-receptor antagonism can increase the number of circulating immune cells and cytokines, e.g. see review by Colucci et al. (2017). These observations illustrate how the endocrine, immune and central nervous systems can work together, and also provides one mechanism by which NMDAR hypothesis of schizophrenia could be expanded to accommodate immunological features. It is proposed below that an immunological explanation of negative symptoms seems also possible and may be particularly relevant to TRS.

1.9 STM, WM, Executive Function and Fluid Intelligence

A variety of models and terms have been used in relation to working memory and attention. Therefore, this section will examine the overlapping concepts of STM, WM, executive function and fluid intelligence. It also highlights cognitive control and selective attention exercised by a central executive or central executive network (CEN). In some accounts cognitive control seems synonymous with "attention" (not necessarily selective attention) or, perhaps, a "controlled processing capability" exercised by the DLPFC and similar to fluid intelligence (Engle et al., 1999). Finally, this section introduces the idea of STM as "activated LTM" and how this may relate to processes involved in synaptic plasticity.

1.9.1 Short-Term Memory, Working Memory and Executive Function

The terms working memory (WM) and short-term memory (STM) are sometimes used interchangeably in the literature, but STM as a construct may be best viewed as a subset of working memory (Engle et al., 1999). Also, while there appears to be a large degree of overlap between "working memory" and "executive function" some executive functions may place no or minimal demands upon memory, for example, the inhibition of pre-potent responses. The meta-analysis by Minzenberg et al. (2009), which included a wide range of paradigms[26] observed a similar network is activated across tasks requiring executive function.[27] Working memory processes specifically associated with the n-back task involve the maintenance, manipulation and updating of remembered information, along with on-line monitoring of operations (Glahn et al., 2005, p.62; Owen et al., 2005, p.47).

Executive function has been broadly defined as: "processes necessary to control or regulate other cognitive processes in the service of goal-directed behaviour" (Minzenberg et. al., 2009, p.812). Maintaining task goals and following necessary processing steps is clearly vital and may be under the control of attention - as assigned to the limited capacity central executive in the multicomponent model which originated with Baddeley and Hitch (1974). Since then, further executive functions have been added to the central executive, as

[26] The meta-analysis comprised 19 n-back studies and 21 other studies of executive function: Oddball paradigm, sequence recall, Stroop, Wisconsin Card Sorting and Word Generation. While not all medication details were available, clozapine use appears to have been very limited with the exception of a study by Jansma et al., 2004 where 8/10 participants received clozapine and 2 received olanzapine.

[27] "Within-group analysis of all of the 41 studies indicated that healthy controls and schizophrenic patients activated a similarly distributed cortical-subcortical network while performing executive tasks, including the DLPFC, ACC, VLPFC, premotor cortex, lateral temporal cortical areas, parietal areas, cerebellum, and thalamus." Minzenberg et al., 2010, p.818.

enumerated by St. Clair-Thompson and Gathercole (2007), these include: temporary activations in LTM, scheduling multiple tasks, switching between tasks, the operation of selective attention along with the ability to inhibit information. Miyake (2000) suggested the following were particularly important: shifting between tasks and information sets, monitoring performance and updating information in working memory, inhibiting dominant or automatic responses.

Following Menon and Uddin (2010) and Crittenden et al. (2015), it is suggested here that shifting between tasks and information sets is likely to involve the dynamic interaction of three large-scale networks: the central executive network, salience network and default mode network. Further, it seems widely accepted task monitoring is likely to engage the ACC in a fairly automatic way using feedback processes and prediction error until an error, or a salient stimulus, engages the attentional processes of the central executive network (Kerns et al., 2005; Carter and van Veen, 2007; Heilbronner et al., 2016). The updating function is classically required by the n-back task, although there may be a debate about how this is achieved: this might be through rehearsal using the phonological loop or the visuo-spatial sketch-pad; alternatively, it might involve maintaining representations through focused attention boosting activations above threshold (Engle et al., 1991). If none of these strategies are efficient, then it is suggested here a mix of strategies could be tried, including reliance on familiarity, possibly based on trace decay. The inhibition of dominant responses, discussed by Miyake (2000), may gain greater prominence at a later stage of processing, however, it is inhibition of distractors and partially activated representations at the encoding and maintenance stages that was regarded as "critical" to WM capacity by Engle et al. (1991). An example of the potentially deleterious impact upon working memory of failing to inhibit distractors and selectively attend to relevant information can be found in Conway et al. 2001 (section 1.10.3), with the caveat this may not be problematic when task demands are within capacity.

1.9.2 Multicomponent Approaches to Working Memory/ Executive Function

One of the strengths of the components approach of Baddeley (2010; 2012) and Baddeley and Hitch, (1974) is its simplicity. This has highlighted processes and capacity limitations, while assessing compatibility with emerging evidence. The original concept of Baddeley and Hitch (along with a visuo-spatial sketch-pad and phonological loop) involved a central executive, representing the well-learned/automatic and controlled aspects of attention, particularly, in relation to actions which built upon the work of Norman and Shallice (1986). More recently Baddeley (2012) has commented it is "increasingly clear that the loop can

also provide a means of action control." When the association with action is considered, this may help to explain why so much of the premotor cortex, BA6, is activated bilaterally in n-back tasks which require a simple button press. Afterall, the brain continually receives information from internal and external sources. It has been proposed this information may cascade in both directions (top-down, bottom up), possibly, in the manner of distributed interactive activation where there are inhibitory links between competing features or representations at different levels (e.g. letter features, letters, words), also between levels (McClelland and Rumelhart, 1981; McClelland and Rogers, 2003) to prime perception, understanding and potential responses. Processing may also be facilitated by the "top-down" biasing of filters through cognitive control (Miller and Cohen, 2001).

These models suggest the links between perception, thought and action may be very close indeed. However, it is also the case that BA 6 is proximal to the DLPFC so activations may be related to this area which in earlier studies was directly associated with short-term memory, for example, "memory fields" were inferred on the basis of cellular recordings in monkeys during delayed response paradigms (Goldman-Rakic, 1995). The DLPFC in conjunction with parietal areas is now more generally conceived as a "multiple-demand system" which is closely allied to fluid intelligence (Duncan, 2010).

Baddeley (2000) added a fourth component to the Baddeley and Hitch (1974) model to account for prose comprehension in the form of an "episodic buffer" which enables the integration of information represented in different codes, for example, spatial and verbal codes from the visuo-spatial sketch-pad and phonological loop, or from LTM. It was further proposed this might be used to model the environment and construct new representations. However, the episodic buffer was subsequently described as an "essentially passive structure on which bindings achieved elsewhere can be displayed" but where "executive processes" can manipulate information (Baddeley, 2012, p.17). One view of the evidence from visual perception is that the brain samples the environment and largely "constructs" what it perceives by drawing upon longer term representations (Cohen et al., 2016), so something like an episodic buffer could be involved. Baddeley has generally been constrained in mapping functions and structures to anatomy although, it was proposed the phonological loop was associated with BA 40 and BA 44, while the visuospatial sketchpad might involve BA 6, 19, 40 and 47 in the right hemisphere (Baddeley, 2000). It is ventured here, the functions "episodic buffer" and the processing of multiple codes, might be conducted in the striatal-thalamo-cortical loops, involving the AST and DLPFC. However, the concept of an episodic buffer needs further support.

1.9.3 Short-Term Memory as Activated Long-Term Synaptic Representations

Some leading theorists appear aligned with the proposal that STM may be instantiated through activated long-term representations (Cowan, 1995; 2005; Engle et al., 1999). This may have originated with Ruchkin et al., 2003, after co-activations were observed in the posterior areas associated with comprehension, visual cortex and prefrontal cortex. The idea, however, was explicitly rejected by Baddeley (2000), along with a proposal "that the slave systems merely represent activations within the processes of visual and verbal perception and production" p.422. Baddeley did assimilate the observations of Gathercole (1995) who demonstrated long-term lexical knowledge influenced the immediate recall of nonwords, commenting this suggested that "information flows from LTM to the [phonological] loop as well as the reverse" (Baddeley, 2012, p.11). However, the role of LTM in STM was circumscribed:

For example, memory for a telephone number spoken in your native language is substantially better than that for a number spoken in a foreign language, reflecting the importance of long-term phonological knowledge in short-term verbal memory. The capacity to remember and repeat a string of unrelated words is about five items, but if they comprise a meaningful sentence, the span is around 15 words, reflecting a contribution from grammar and meaning, both depending on different aspects of long-term memory. (Baddeley, 2010, p.140).

Nonetheless, the idea of STM as "reactivated LTM" could map readily onto biological substrates at the synaptic level, for example, with short-term plasticity and transient activation of existing representations reflected in inhibitory and excitatory postsynaptic potentials; for example, Cowan (1995) defined working memory as "the set of activated memory elements." (p.100) and in their model elements (or microfeatures) are at different stages of activation and are subject to trace decay if they are not boosted, for example, through the application of capacity-limited attention. Further, as discussed by Engle et al. (1999), even when activations are outside conscious awareness, they may influence perceptual and semantic processing. Also, Eriksson et al. (2015) observe, working memory "may involve short-term plasticity ... it works by recruiting already existing synapses and ion channels ("activated LTM")." (p.34) By contrast, longer term changes to memory involve protein synthesis and occur over a longer time-course (Friston, 2002). In section 1. 5. 5 on synaptic plasticity an example of the precision that may be required can be found by reference to Xu and Yao (2010) who described how changes may be achieved through the temporary lifting of tonic inhibition in pre- and post-synaptic circuits.

1.9.4 The Relationship between Working Memory and Fluid Intelligence

A distinction between crystallised and fluid intelligence is reflected in the subscales of the WASI (section 2.7.1). It is also clearly made in Baddeley's (2012) model with crystallized knowledge segregating with visual semantics, language and episodic LTM, while the sketch-pad, phonological loop, and episodic buffer, along with the central executive, form the working memory system which aligns with fluid intelligence (Figure 3 in Baddeley, 2012, p.16). Consistent with this, it is further observed that WM is "represented by a series of fluid systems that require only temporary activation" while LTM represents "more permanent crystallized skills and knowledge." p.11. Examples of "fluid" operations include planning, chunking or aggregating information, perceptual grouping, the use of imagery, updating and temporal sequencing. Importantly, this division was also supported by a latent variable analysis conducted by Engle et al. (1999), whose study of 133 healthy participants affirmed STM as a subcomponent of working memory and observed working memory was strongly related to fluid intelligence, whereas short-term memory was not. The point was reinforced in Joyce (2013), who observed "The cognitive requirements of tests of fluid intelligence overlap considerably with those of executive function." (p.162). Moreover, functional neuroimaging studies have indicated the areas involved in cognitive control are also active in tests of fluid intelligence (Gray et al., 2003; Duncan, 2010). Therefore, when considering the correlates of performance IQ in this study, the terms "executive function", "cognitive control" and "fluid intelligence", refer to a similar underlying construct. Further, applying Baddeley (2012), it is assumed VIQ scores will be strongly influenced by lexical knowledge in LTM, while PIQ scores will be strongly associated with fluid intelligence.

1.10 Translating Neurobiology to Symptoms

Kapur's (2003) conception of dopamine as a learning signal which confers "motivational salience" upon internal representations and external stimuli and events, may have resonated with thousands of clinicians who have witnessed the increased drive into sensory and motor circuits during an episode of psychosis as reflected in "pressure of speech", flight of ideas, hyperlocomotion and agitation. Consistent with the idea of "salience", phenomenological experiences of visual and auditory hyperacuity have also been reported (Kelemen et al., 2013). Even more pertinent, perhaps, is Grace's (2010; 2016) observation that chronic hyperactivity in the dopaminergic cells of the VTA would mean that exaggerated responses would be given to stimuli, thereby conferring salience.

Many accounts are now attributing symptoms to impaired connectivity. This found eloquent expression in Friston and Frith (1995), who proposed that while pathology

localised to areas like the DLPFC might explain some symptoms of schizophrenia, "abnormal interactions or the integration between different cortical areas" may also have explanatory power. (p.92) Further, it was assumed that "the frontal cortices are necessary for intrinsically generated behaviour." (p.93) In doing so they drew upon a wealth of neurological, neuropsychological and preclinical studies; for example, analogies were made between "psychomotor poverty" in schizophrenia which may include decrements in vocalisation, flat vocal expression, social withdrawal or diminished facial expression, with the kinds of symptoms observed in degenerative or acquired frontal lobe damage involving the ACC and/or supplementary motor area. Also, deficits in executive function have been observed following frontal lobe damage: for example, in a study that compared 26 individuals with unilateral or bilateral lesions with age and IQ matched controls, individuals with frontal lobe lesions needed more time and were more impaired on a test of spatial working memory (Owen et al., 1990). Further, in this study, individuals with frontal lobe lesions appeared less able to improve performance through the use of strategy which might be related to the impaired monitoring of behaviour as proposed by Frith (2008).

However, negative and other symptoms might be also explained by deficits in the functioning of frontal-striatal loops where information is integrated and the willed initiation of behaviour (which might be informed after consultation with long-term memory involving other networks e.g. Frith, 1987; Davey et al., 2016; Kaminiski et al., 2017; also reviewed by Robbins, 1990). Frith (1987) had suggested both positive and negative symptoms might arise from impairments in willed intentions which are not correctly monitored and can lead to behavioural symptoms. "Either a patient fails to recognise that an action is the consequence of his own will (positive symptoms), or else the will fails to generate the actions altogether (negative symptoms)." (p.634)
Moreover, this will act as a barrier to better performance in future if it is not possible to recognise what kind of error has been made.

1.10.1 Dysconnectivity and Different forms of Dysconnection

The idea of prediction error, working automatically and continuously below conscious awareness for much of the time, shows how behaviour can be informed and finessed, for example, it can use proprioceptive information to guide and smooth movement. A failure might only be noticed, for example, by missing the last step on the stairs (Marsh, 2014). It may also apply to higher cognitive processes with schizophrenic symptoms being a possible consequence of faulty prediction error and monitoring (Peterburs and Desmond, 2016).

The mechanism for this aberration was proposed by Friston and Frith (1995) to be disconnection. This also finds application to higher cognitive processes as well and, as discussed later, it may lead to failures in error detection which diminishes the prospects of improvement. Other examples might include premature decision making on the basis of inadequate information ("jumping to conclusions"), delusions (where, perhaps, the logic of a situation goes awry); hallucinations (where the source of sensory stimulation may be misattributed). Possibly all served by a strong drive for the brain to interpret sensory inputs, which may be further influenced by cognitive biases and emotional aspects.

Friston and Frith (1995) observed while dysconnectivity may accommodate the diversity of symptoms in schizophrenia, the impaired use of prediction error arising from this need not be incompatible with other explanations (e.g. auditory-visual hallucinations may have more than one cause). Since then, amongst many functions, evidence has mounted that the ACC serves an important role in monitoring for conflict and errors (Carter and van Veen 2007; Ullsperger, Danielmeier, and Jocham, 2014).

The literature on oscillatory rhythms, as applied to schizophrenia, has burgeoned since it has become evident that electrophysiological recordings of local field potentials are not just of interest to sleep researchers and clinicians looking for signs of pathology but reflect an important form of communication that synchronizes and integrates different information streams: oscillatory rhythms may also facilitate long range communication across and between networks, for example, by stimulating and "entraining" patterns of activity in cell populations downstream. Gamma oscillations which represent a broad range of frequencies, may be involved in selective attention (Fries, 2001) and support working memory at increasing levels of cognitive load: for example, Lewis et al. (2004) observed "Studies in non-human primates indicate that normal working memory function depends upon appropriate GABA neurotransmission in the DLPFC, and alterations in markers of GABA neurotransmitters are well documented in the DLPFC of subjects with schizophrenia." (p.143) Further evidence that oscillatory rhythms support working memory performance has come from: Basar-Eroglu et al. (2007), Menzies et al. (2007), Haenschel et al. (2009), Michels et al. (2012), Chen et al. (2014), Roux and Uhlhaas (2014), Senkowski and Gallinat (2015), Yoon, Grandelis and Maddock (2016), So et al. (2018).

Central to dysregulation may be hypofunction of the NMDA receptors on parvalbumin containing interneurons which act together to generate gamma oscillations through feedback inhibition on pyramidal neuron networks. The NMDA receptor antagonist ketamine can elicit positive and negative symptoms at subanaesthetic doses, and also induce deficits in free recall and recognition along with disturbance in attention (Krystal et al., 1994; Xu et al., 2015), which in Malhotra et al. (1996), seemed to be independent of the psychotic symptoms (p.305). Low levels of GABA in the DLPFC of healthy human participants have been associated with a faster deterioration in working memory performance with increasing cognitive load (Yoon, Grandelis, and Maddock 2016); yet studies with ketamine, PCP, MK-801 and other NMDA receptor antagonists have produced dose-dependent increases in baseline gamma in rodents and healthy humans (Driesen et al., 2013).

However, this could be understood in terms of a lack glutamatergic transmission leading to an imbalance with GABA. It might also be compatible with Gandal et al.'s (2012) proposal that increases in baseline activity might increase background noise in processing, making signal detection more difficult. A further aspect to consider are the contrasting gradients of expression of makers of GABA and glutamate in a caudal to rostral direction that have been observed, postmortem in humans, in areas associated with visuo-spatial working memory: where GABA concentrations are at their highest in the primary visual cortex and at their lowest in the DLPFC, while glutamate shows the opposite pattern (Hoftman et al., 2018). Perhaps, GABAergic interneurons help to segment, transmit and integrate information, but processing in the prefrontal cortex is more nuanced, involving a greater role for other neuromodulators, including dopamine. Some convergent support for this view might come from the observation of another gradient which concerns a relatively greater amount of arborisation and dendritic density in the prefrontal cortex. However, this may be a delicate balance as a lack of inhibition may also mean a lack of protection in excitatory networks and decrements in the spine density of pyramidal neurons (rather than neuron loss), especially in deep layer 3 (which along with layer 4 is the main target of excitatory projections from the thalamus), is a well-established observation in schizophrenia (Glausier and Lewis, 2013), for example, in the DLPFC and the auditory association cortex (Pierri et al., 2003; Lewis et al., 2003). Consequential to dendritic loss there will be less glutamatergic transmission. In their comparison of 7 studies of postmortem tissue, Moyer et al. (2015) observed that significant reductions in spine density had been observed in the areas studied in schizophrenia relative to control subjects with a median decrease of 23% (range 6.5 - 66%).

This is also supported by Hoftman et al. (2018) who observed measures for glutamate in postmortem samples were reduced in individuals with schizophrenia, while GABA was elevated. The alterations were in layer 3 which carries glutamatergic projections from pyramidal neurons from region to region: from the primary visual and association cortices (V1, V2) in the occipital lobe to the posterior parietal cortex (PPC) and DLPFC. By contrast, local GABAergic interneurons influence the activity of pyramidal neurons and also generate gamma frequency oscillations. Hoftman et al. (2017) reviewing the literature on layer 3 circuitry of the DLPFC affirmed its importance to working memory. Taking an integrative approach, they concluded alterations may occur during development but many associations with environmental factors suggesting there may be "multiple sensitive periods" when this circuitry may be disturbed because it takes so long to mature. However, Moyer et al. (2015) observed it is the excitatory synapses onto dendritic spines in layer 3 which undergo the greatest pruning during adolescence and proposed this may contribute to early disease onset. Hoftman et al. (2018) tentatively proposed a resolution involving regional differences, so that *deficits "*in both glutamate and GABA neurotransmission in the DLPFC might impair the ability of layer 3 microcircuitry to increase the power of gamma oscillations required" for visuo-spatial working memory function, whereas increases "in glutamate and GABA neurotransmission in layer 3 of V1 [primary visual cortex], might contribute to the elevated levels of visual gamma power reported in psychosis" p. 676 (see Brealy et al., 2015).

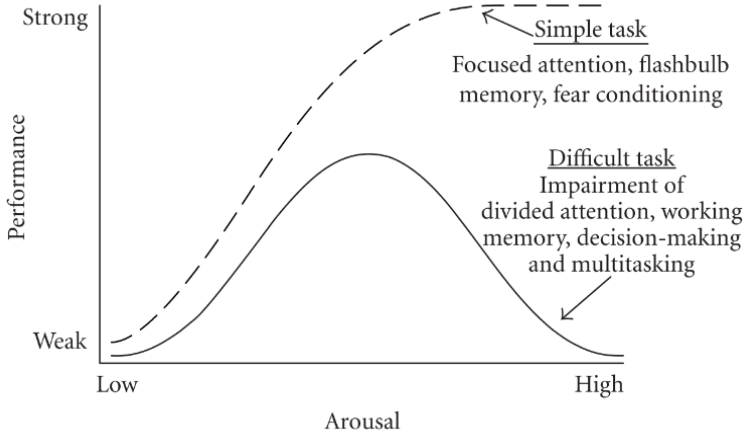
However, further regional specificity is required to accommodate observations made by Kegeles et al. (2010) of elevated GABA and Glx (glutamate and glycine combined) in the medial prefrontal cortex of unmedicated patients compared with controls, which were not present in medicated participants, possibly indicating a normalisation of glutamatergic function with antipsychotic treatment. Moreover, no alterations in the DLPFC were observed in either group, which is at odds with Hoftman et al.'s (2017) postmortem study. The elevation in GABA described by Kegeles et al. (2010) was "unexpected", while in a comprehensive review of GABAergic mechanisms in schizophrenia, (de Jonge et al., 2017) it was acknowledged "the current literature is inconsistent regarding the measured GABA levels in different brain regions." Perhaps inconsistency should be expected if basal concentrations of GABA vary across the brain. A further consideration might be local metabolic demands which may be excessive in certain condition and whether processes which support GABAergic function, for example, synthesising enzymes, can meet these.

1.10.2 Stress, Learning, Executive Function and Memory

A range of neuropsychological and cognitive impairments have been observed in schizophrenia including "executive function" which may underpin aspects of performance in certain cognitive tasks. Closely allied to this, and often referred to interchangeably, is working memory, which enables representations of external stimuli or internally generated representations to be temporarily held in readily accessible form while other cognitive operations are conducted. These might include operations upon the representations themselves, for example, re-ordering items in a sequential list or, perhaps, the rotation of mental images.

Yerkes and Dodson (1908) in their experiments with "dancing mice" correctly noted the effects of stress varied with task difficulty, so that simple tasks were unimpaired at high levels of arousal, as illustrated in the graph below.

Figure 1. 2 Differential Effects of Stress on Simple and Complex Task Performance (Yerkes and Dodson, 1908).



Source: https://upload.wikimedia.org/wikipedia/commons/b/ba/OriginalYerkesDodson.JPG Also see Diamond et al. (2007): The temporal dynamics model of emotional memory processing.

Arnsten (2009) vividly discusses differential effects of stress upon task performance in humans observing that "Some of the first studies on the effects of stress on cognition began after the Second World War, based on observations that pilots who were highly skilled during peacetime often crashed their planes in the stress of battle owing to mental errors". Further, that early studies in this area revealed stress can impair task performance where complex and flexible thinking is required but that it can also improve the performance of "simpler and/or well-rehearsed tasks". The kinds of tasks that were impaired by stress were

those that involved the influence of PFC operations (Arnsten, 1998), "whereas engrained habits that rely on basal ganglia circuits were spared or enhanced." p.410 These also indicated the locus of control had an effect so that if individuals felt (sometimes wrongly) they were in control of the situation they were often unaffected by the stress. Considering stress/arousal (as shown on the horizontal axis of the Yerkes-Dodson graph above), cortisol or ACTH could replace the label, but it suggested that any of the catecholamines that are released in response to the activation of the HPA might also be substituted, i.e. dopamine, norepinephrine, epinephrine. A further consequence of HPA activation is the release of energy resources into the circulation in the form of triglycerides (lipids) and glucose, but dysregulation in the form of hyperglycaemia or insulin resistance might, perhaps, undermine the efficiency of HPA activation at the cognitive and behavioural levels.

1.10.3 The Category of Symptoms is not Closed: Perception and Cognition

Notwithstanding the extensive symptoms described above, the list is incomplete as perceptual problems are frequently omitted from discussion, even though they could potentially impact upon higher processing - including the quality of representations, for example decreasing visual contrast or components of the orthographic structure can prolong naming times (Frederiksen and Kroll 1976; Mechelli et al., 2000). Ophthalmology issues have been reviewed by Gracitelli et al. (2015) who noted decrements in the thickness of retinal nerve fibre layer and macular areas have been observed in schizophrenia, Alzheimer's Disease and Parkinson's Disease. In addition, Lee et al. (2013) found a positive correlation between the extent of thinning and illness duration. Citing their own work, Gracitelli et al. (2015) commented that abnormalities in the magnocellular pathway, which conveys lower spatial frequency information from the retina to the visual cortex, are well-established in schizophrenia and "the neurophysiology of these processes involves deregulation of glutamatergic activity to dopamine receptors and interactions between magnocellular and parvocellular pathways." p.10

The parallel and complementary nature of these pathways has been described by Denison et al. (2014): the magnocellular neurons of the lateral geniculate nucleus are suited for motion detection and "other rapid visual changes occurring at large spatial scales" while parvocellular neurons are specialised for "detailed form and color processing," p.1053 Gracitelli et al. (2015) elaborate further observing the magnocellular pathway is suited to low light conditions, "stereopsis, spatial localization, depth perception, hyperacuity, figural

grouping, illusory border perception, and figure/ground separation" while the parvocellular pathway conveys detailed, high frequency information about static objects.

It follows that abnormalities in the magnocellular pathway may deprive the brain of useful information and, as processing is faster along this route, it may also normally help to "prime" other processes. Some support for this may be found in Nunez et al. (2013) who describe priming as "highlighting of relevant information" and suggest it is "critical for orienting attention in space preferentially to parieto-occipital and other dorsal stream visual areas." Electrophysiological measurement of the N80 amplitude indicated participants with an early age of onset of schizophrenia (mean 16 years; 13-18) did not benefit from a priming effect from the magnocellular pathway in their pattern reversal paradigm, however, a group with a later age of onset (mean 32 years; 26-38) and controls did. The difference in the early onset group was interpreted as being compatible with a neurodevelopmental hypothesis of schizophrenia.

Magnocellular abnormalities have also been inferred in schizophrenia concerning the perception of motion (Kandil et al., 2013); reading (Martinez et al., 2012); and the perception of facial emotion (Jahshan et al., 2017), which might surely impact, in turn, upon the development of skills related to social cognition? Shared perceptual deficits in individuals with schizophrenia and unaffected siblings have been observed (Keri et al., 2004; Keri et al., 2005) and also in unaffected parents (Gracitelli et al., 2013), thereby indicating these may reflect a heritable endophenotype of schizophrenia.

Perceptual deficits of a different kind have been reported by Yoon et al. (2010) who observed a 10% reduction in the major inhibitory transmitter GABA in the visual cortex of medicated individuals with schizophrenia of a recent onset in conjunction with reduced contrast discrimination (indexed by orientation-specific, surround suppression of contrast gratings). Kelemen et al. (2013) also found reductions in GABA levels, relative to healthy controls, in 28 FEP participants before medication and 8 weeks after treatment with antipsychotics (only 3 were treated with conventional antipsychotics). Contrast sensitivity improved with treatment (sensitivity was actually reduced but it was inferred there had been hyperactivity in the magnocellular retino-geniculo-cortical pathways). "Anomalous perceptual experiences" were also reduced - these were not hallucinations but involved "disturbingly high intensity of environmental stimuli", possibly equating to sensory hyperacuity where stimuli present with a higher level of detail and intensity than normally experienced. However, treatment failed to normalise performance on a test of motion perception where performance was abnormally superior.

Kelemen et al. (2013) had expected to replicate the correlation between changes in visual function and GABA levels in the occipital cortex observed by Yoon et al. (2010), thinking this would be consistent with deficits in gamma oscillations observed in schizophrenia and their potential relationship with glutamatergic hypofunction and working memory deficits (Lewis and Gonzalez-Burgos 2006), however, this was not supported. It was suggested a methodological difference may have accounted for the correlation in Yoon et al. (2010). Also, the participants in Yoon et al. varied on some parameters and illness stage as well as medication or region could be important, for examples, elevations in GABA had been observed in the parieto-occipital cortex of individuals with chronic schizophrenia by Ongur et al. (2010), who found no difference between individuals taking atypical and typical antipsychotics; while in a study by Kegeles (2012), 16 participants with long-standing illness who were unmedicated (9 were medication naïve) exhibited elevations in GABA, along with glycine and glutamate in the medial prefrontal cortex, but not the DSFPC. Whereas those who were medicated (n =16) with atypicals for at least 4 weeks, did not show increases. The FEP participants in the study by Kelemen et al. (2013) had reduced levels of GABA in the visual cortex relative to controls both at baseline and after antipsychotic treatment).

The focus on medication is important as antipsychotics can have pronounced effect on D2 receptors in the retina and affect sensitivity to contrast gratings (Harris et al., 1990), enhancing sensitivity to low spatial frequency while reducing sensitivity to medium and high spatial frequency information. This mirrors the pattern with hypodopaminergia in Parkinson's Disease which is reversed for medium spatial frequencies by dopaminergic drugs (Domenici et al., 1985). It is interesting that only 3/28 of the clinical participants in the study by Kelemen et al. (2013) were receiving treatment with conventional neuroleptics (and 1/13 in the study by Yoon et al., 2010) yet there may have been an effect on dopamine function in the retina).

While antipsychotic treatment may be a complicating factor, such research could lead to the development of "state" or "trait" biomarkers based on perceptual tests, as explored by Koychev et al. (2011). However, the attribution of such observations to the magnocellular pathway has been challenged by Herzog and Brand (2015) on the basis this is unproven. (They also criticised the methodology of Keri et al., 2004, 2005 above). Kelemen et al. (2013) agree "the exact psychophysiological distinction of the M and P pathways has been debated." However, the evidence of dysfunction in the magnocellular pathway reviewed by Gracitelli et al. (2015) is derived from more than one methodology. Nonetheless, Herzog

and Brand point to a rich evidence on masking paradigms in schizophrenia research, including, observations made by Slaghuis et al. (1995) that individuals with a higher level of negative symptoms needed a longer period to process target stimuli and were more sensitive to backward masking. Indeed, backward masking may bear a relationship to sensory gating - an issue explored by Wynn et al. (2004) who wondered if they index a common factor. Individuals with schizophrenia exhibit slower recovery from backward masking and deficits in pre-pulse inhibition (PPI). Wynn et al. (2004) suggested higher levels of PPI may help to "gate out" the disruptive effects of backward masking so clinical participants would be disadvantaged.

At the end of this complicated story where it might be wondered if medication effects on retinal dopamine cells might explain deficits in backward masking, or imbalances between the magnocellular and parvocellular streams of information, there is still the evidence relating to perceptual abnormalities in first-degree relatives, also, the phenomenological accounts of non-hallucinatory perceptual distortions before any medication is taken. The observations of abnormal levels of GABA in different brain regions and at different stages of the illness also needs to be explained. In addition, there is interest in considering the role of GABA in sensory gating (Cheng et al., 2016).

Moreover, corresponding deficits in PPI have been observed in the auditory realm, for example, correlations between auditory and visual PPI were observed in the study by Wynn et al. (2004). As described for putative abnormalities in the magnocellular pathway, deficits in auditory sensory gating might affect higher level processing; for example, difficulty in the pre-attentive detection of subtle alterations in speech sounds was observed in schizophrenia by Kasai et al. (2002). These issues may assume greater relevance to TRS, when the performance of participants in this study on a Continuous Performance Task and also the Hopkins Verbal Learning Task are considered.

It was proposed above that deficits in early sensory processing in various modalities, including those potentially related to abnormalities in GABAergic transmission, are usually overlooked although they form part of the symptomatology of schizophrenia. However, there may be further ramifications which affect higher level processes; for example, upon the efficiency of encoding which might, in turn, affect the number of items that can be held in capacity-limited stores such as working memory. This may underlie the phonological similarity effect (Conrad 1964), visual similarity effects (Saito et al., 2008) and the word length effect (Baddeley, Thomson, and Buchanan 1975) where the quality and parsimony of encoding appears to reduce the number of items recalled in short-term memory tests.

The clarity of an auditory signal against background noise will affect the quality of the information that converges for processing in the striatal-thalamo-cortical loops, but before it even enters neural pathways, the quality of the signal will also be influenced by the way attention is deployed, filtering out or inhibiting some aspects and selectively attending to others. This was illustrated by a study by Conway et al. (2001) which simulated "the cocktail party phenomenon" and observed that individuals with higher working memory spans were less likely to detect their names in an unattended stream of information than those with lower spans. This was interpreted as indirect evidence of more effective inhibition of irrelevant information by individuals with higher spans, however, it was observed the result could so easily have gone in the opposite direction, with individuals with spare capacity being better able to monitor the environment.

1.10.4 Do Negative Symptoms Resemble Sickness Behaviour?

Immune activation has been observed to affect behaviour, for example, during immunotherapy in cancer treatment. Capuron et al. (2005) commented "a rich database has been developed that substantiates the capacity of proinflammatory cytokines, including tumour necrosis factor α, interleukin (IL-1 and IL-6), to induce behavioural symptoms referred to as "sickness behavior." p.2 This is typified by social withdrawal, fatigue, anhedonia and, perhaps, depression. There is some debate as to whether withdrawal is about finding a place of safety, away from predators while energy resources are directed toward recuperation and repair, or whether this confers benefit to a group by containing the risk of disease transmission. Quite possibly both arguments might apply.

These behaviours were observed in sick animals by Hart (1988) and has subsequently been extended to humans, especially in relation to depression (e.g. Raison, Capuron, and Miller 2006; Dantzer 2009). Sickness behaviour may include a lack of appetite, activation of the HPA axis, a reduction in parasympathetic tone, disrupted sleep with less REM and more slow-wave sleep, a flattening of diurnal rhythms (for example of cortisol production), impaired learning and memory for recent events (Dantzer et al., 2008). It is unclear whether this has been directly commented upon, apart from Smith (1992) below, but, at first sight (with the possible exception of reduced appetite), surely there is similarity between "sickness behaviour" and the negative symptoms of schizophrenia?

The theory that immune activation might have psychological effects originated with Smith (1991) and Maes et al. (1995), based on observations of elevations in cytokines in depressed

individuals. Dantzer et al. (2008) commented on the originality of the hypothesis "especially at a time when depression was thought to be associated with decreased rather than increased immunity." p.4 Then, Smith (1992) extended the theory to schizophrenia:

Recently I proposed excessive production of interleukin-2 (IL-2) and IL-2 receptors (IL-2Rs) by gastrointestinal (GI) T-lymphocytes as the cause of schizophrenia (10, 11). The idea for the hypothesis was initiated by the well documented, but profoundly ignored, observation that IL-2, when given to psychiatrically normal human volunteers, produces severe positive and negative symptoms of active phase schizophrenia in the majority of subjects (12). Once the importance of this clinical observation is realized, then an astonishing amount of previously unexplained information on schizophrenia becomes coherent. The negative symptoms (apathy, avolition. alogia, emotional flattening, asociality), which are identical to symptoms of depression, usually occur throughout the disease. (p.249)

Consideration of such aspects has been slow to gain traction. Indeed, the eminent neuroscientist, Ed Bullmore (2018) has commented that psychoimmunology has only recently started to gain acceptance (after refutation of an established idea that the brain has "immune privilege", which virtually prevents all such activity beyond the blood-brain-barrier). The book highlights the similarities between depressive symptoms and those of sickness behaviour and points to evidence that immunotherapy may have great potential in their treatment. It is not suggested explicitly there is overlap between the symptoms of sickness behaviour and negative symptoms but closing pages indicate immunotherapy could be successfully applied in schizophrenia. The book is essentially a "call to arms" with Bullmore warning "it may never happen" unless these ideas are followed up. Fortunately, it has received many commendations.

But what of TRS? If there is indeed a link then the persistence of negative symptoms would suggest TRS should be a good candidate for this approach. Recent studies have reported elevations in inflammatory cytokines in FEP individuals, also in individuals with long-standing psychosis (Di Nicola et al., 2013; Mondelli et al., 2011). Moreover, in a study which combined measures of inflammatory markers with waking cortisol levels, Mondelli et al. (2015) observed reductions in cortisol and inflammatory cytokines after 12 weeks of treatment with antipsychotic medication in participants who responded to this treatment but not in non-responders. Interferon gamma (IFN-γ) was strongly related to the severity of negative symptoms at both time points.

1.10.5 Might Negative Symptoms and Cognition be Related?

Several studies have observed that negative symptoms may persist along with cognitive deficits. Impaired cognitive function and psychosocial adjustment have been associated with worse functional outcomes in the community (Green, Kern, and Heaton, 2004; Iasevoli et al., 2016). However, one study observed attention, working memory and verbal fluency predicted functional outcomes in schizophrenia even when negative symptoms were controlled for (Jaeger et al., 2003). Cognitive deficits are so common they are regarded by some as a core symptom of schizophrenia; however, they were not regarded sufficiently specific for diagnostic purposes in DSM-5 (Tandon et al., 2013). This might be revisited if TRS is accepted as a sub-category, for example, de Bartolomeis et al. (2013) observed worse performance on a verbal memory task in their TRS participants than "non-TRS" participants. In addition, worse performance was associated with a higher level of negative symptoms in the TRS group, leading them to suggest cognitive deficits in TRS might be related to negative symptoms (also see Jaeger et al., 2003).

Some researchers have divided negative symptoms into further dimensions described as "diminished emotional *expression*" (blunted affect and alogia[28]) and "apathy" (anhedonia, avolition and asociality) - which may also be referred to as diminished emotional *experience*. Hartmann-Riemer et al. (2015) found diminished emotional expression was significantly associated with verbal learning and memory, planning and a composite cognitive score when variation relating to severity of apathy was held constant. While none of the cognitive measures correlated with apathy when diminished emotion expression was held constant. By contrast, Harvey et al. (2017) , found that apathy predicted social outcomes better than DEE or negative symptoms. Therefore, associations between negative symptoms and cognition or psychosocial outcomes may be influenced by the precise nature of the symptoms.

Improvements in negative and cognitive symptoms (especially those relating to executive functions) have been observed in case reports when antipsychotic treatment has been augmented by the antibiotic minocycline, as reviewed by Zhang and Zhao (2014): in an open-label study using minocycline as an adjunctive, Miyaoka et al. (2008) observed

[28] **Blunted Affect**: diminished emotional expression - reduction in facial expression and communicative gestures. If present, these may seem "forced, artificial or lacking in modulation".
Alogia: poverty of speech (or, as Blanchard and Cohen (2006) prefer "poverty of content of speech" which aligns this with "lack of spontaneity and flow of conversation" (item N6 on the PANSS), and not G7, motor retardation.

improvements in 22 participants on all PANSS subscales after 4 weeks without adverse effects. (The participants had been unwell for a mean of 4.9 years (1-15 years).

These results are also consistent with a randomized, double-blind, placebo-controlled study investigating the effects of minocycline augmentation which started in 2003 and was reported by Levkovitz et al. (2010). With further corroboration from a parallel study which concerned 78 individuals with "early-phase" schizophrenia, receiving atypical antipsychotic medication (including clozapine), of whom 54 also received minocycline. After six months of adjunctive treatment, improvements in general outcome (global impression), negative symptoms, working memory and other cognitive aspects were observed. These results have been replicated in a larger double-blind randomised placebo-controlled study with respect to improvement in negative symptomatology. The evidence concerning cognitive symptoms was less clear, but difficulties in finding equivalent tests with appropriate standardisation may have been a factor as the research was conducted in Pakistan and Brazil (Chaudhry et al., 2012), while the study by Levkovitz et al.(2010) was conducted with Israeli participants.

Following, their earlier 2014 review, Zhang et al. (2018) have published a double-blind randomised placebo-controlled trial with 75 schizophrenia participants with elevated negative symptoms, conducted in China. After 3 months of treatment with risperidone and minocycline, greater improvements for negative symptoms were observed in participants who had received a high dose of minocycline than those who had received a lower dose or placebo. It also correlated with reductions in interleukin-1beta and IL-6 in serum. While the evidence in relation to cognitive symptoms may be weaker, all these studies provide persuasive evidence of inflammatory cytokines being related to negative symptoms.

Associations between negative symptoms and specific inflammatory cytokines may be especially pertinent to TRS in view of the persistence of negative symptoms and higher level of suicide attempt. Moreover, Zhang, Zhao et al. (2005) cited studies which indicated that abnormalities in inflammatory cytokines had been "particularly prominent" in TRS. This was supported by their own research with Chinese participants considered to be TRS where elevations in interleukin 6 were observed after a 2-week washout period relative to healthy controls. Elevations were also observed in cortisol at baseline and correlated with negative symptoms. They were also correlated after 12 weeks of antipsychotic treatment with haloperidol or risperidone, when significant reductions in cortisol and negative symptoms were seen. The interpretation of IL-2 and IL-6 was more complicated as they were not detected in some participants and intercorrelations were not significant. Interestingly, elevations in IL-2 were associated with positive symptoms although this was

not reported in a study of 68 FEP participants by Mondelli et al. (2015) who did however find persistent elevations in Interleukin-6 were associated with non-responsiveness to first line antipsychotics. Decrements in the cortisol awakening response (CAR) and higher interferon-gamma were also observed in the non-responders from the outset. Mondelli et al. (2015) observed, "The blunted CAR and the reduced HPA axis reactivity to stress have also been associated with more severe symptoms and worse cognitive function in patients with psychosis. Furthermore, the blunted CAR is not normalized by antipsychotic treatment, indicating that it may represent a stable biological feature of psychosis." (p.2) Therefore, their suggestion that cortisol and inflammatory cytokines could serve as biomarkers to predict treatment response and point to new therapies appears well-founded.

This set of results is also interesting from an endocrine perspective, as according to Rotter et al. (2003) associations between IL-6 and insulin resistance have been demonstrated in several studies. Fat cells appear to be targets for Il-6 and TNF-alpha which both appear to decrease "insulin-stimulated glucose transport." In a study of cultures of human fat cells, Rotter et al. (2003) observed TNF-alpha amplified IL-6 production. Moreover, there was also a 15-fold elevation in TNF-alpha and IL-6 cells from a subgroup non-obese of insulin-resistant individuals. Given the metabolic liability of clozapine, this surely highlights the importance of attempting to control hyperglycaemia even in the absence of overt diabetes. Moreover, it would be interesting to ascertain if immune treatments might improve insulin sensitivity as well as bringing about an amelioration in negative and cognitive symptoms. Further evidence for an association between immune activation and cognitive deficits comes from preclinical studies where behavioural responses to the endotoxin lipopolysaccharide, found on the membrane of gram-negative bacteria, have been reported to include a reduction in social interactions and worse memory for objects by adult rats that had been injected with a toxin when pups (Zhu et al., 2014). "Dramatic" elevations in microglia were observed in the hippocampus, thalamus and cerebral cortex of the adult rat, but reductions were observed if they were subsequently treated with minocycline, risperidone, or in combination. Moreover, there were corresponding improvements in behavioural measures of prepulse inhibition, memory for novel objects and social interaction.

In one functional neuroimaging study of patients receiving interferon-alpha therapy, which "is notorious for causing behavioural symptoms, including depression, fatigue and cognitive dysfunction" (p.190), increased activity was observed in the dorsal ACC relative to control patients who were not receiving this treatment. There were no significant differences in performance of visuospatial attention task but there was a strong correlation between ACC

activation and the number of errors in the immunotherapy group who may have been having to work harder (Capuron et al., 2005)

This simple interpretation is based on a view that various negative symptoms are not conducive to learning or the energy expenditure associated with cognitive effort. Another might be related to weaker connectivity with the reward circuitry which could undermine motivation.

1.10.6 Are Negative Symptoms related to Default Mode Activity?

Another association with negative symptoms could relate to hyperactivity in the default mode network which has been observed in some medical conditions for example, instantiated in increased strength of connectivity in the resting state. Under these circumstances, the "default" position might be a heightened tendency for attention and cognition to revert to the inner world.

The relationship between the DMN and CEN appears to be influenced by NMDAR function. Anticevic et al. (2012) demonstrated the connectivity and strength during a delayed working memory task was altered by the administration of ketamine to healthy participants. The extent of this disruption predicted task performance and transient symptoms were observed that resembled schizophrenia (although only the relationship between the degree of DMN deactivation and negative symptoms was significant, indicating greater DMN activity/failure to supress was associated with a higher level of negative symptoms). It is suggested here, the weakening of segregation between major networks, might help to explain aspects of abnormal states which describe an increased "oneness" with the universe - where boundaries between the external and inner worlds disappear.[29]

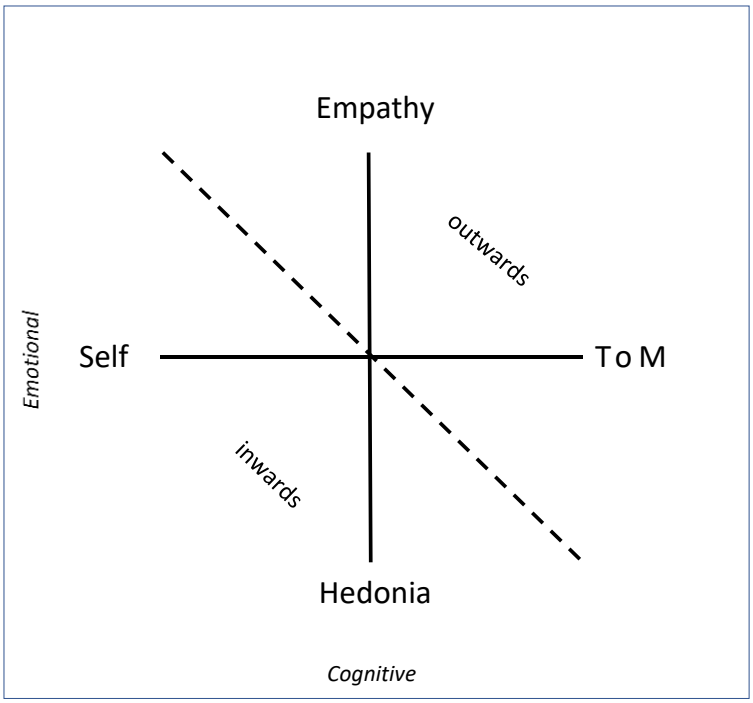
The idea of major networks relating the inner and outward worlds (for example the DMN and CEN respectively), also finds resonance with Nekovarova et al. (2014), who have proposed Menon's triple network theory might be applied to diverse symptoms of schizophrenia. Choosing as the bedrock of their model, the ability to construct

[29] This idea finds expression in studies concerning the psychedelic drug psilocybin (e.g. Carhart-Harris et al., 2012; Tagliazucchi et al., 2016). A pharmacological description by de Gregorio et al. (2016) indicated different effects according to dose: "LSD's mechanism of action is pleiotropic, primarily mediated by the serotonergic system in the Dorsal Raphe, binding the 5-HT2A receptor as a partial agonist and 5-HT1A as an agonist. LSD also modulates the Ventral Tegmental Area, at higher doses, by stimulating dopamine D2, Trace Amine Associate receptor 1 (TAAR1) and 5-HT2A."

representations of ourselves and others to understand mental states, they regard emotional flattening "a core negative symptom of schizophrenia" which interferes with this process, affecting inward aspects (anhedonia) blunted affect/ diminished emotional expression (N1) and outward aspects relating to a lack of empathy or poor rapport (N3). They propose the domains of the "self" and feelings of pleasure are associated with an inward direction of reference, while those of empathy and perspective taking/ "theory of mind" (ToM) are related to an outward orientation. Also, self-awareness, involves the representation of one's own mind and self-reflection enables inferences concerning the thoughts of others. Similarly, autobiographical memory may inform, including anticipation of the future and "underlies representations of one's own mental states, a process parallel to … ToM." (p.2) Nekovarova et al. (2014) propose that in schizophrenia "deficits in coordination" of the triple network may underlie functions related to the "self" leading to impaired social cognition. Their model, only superficially described here, and reflected in the diagram below[30], extends understanding of the potential nature of negative symptoms, especially in relation to social cognition by highlighting differences in perceptions relating to the inner and outer world.

Figure 1. 3 Perspectives from Inner and Outer Worlds

After Nekovarova et al., 2014



[30] Figure 1 .3 depicts a "cognitive dimension" (self : theory of mind) and a second dimension "with stronger motivational accent" (empathy : hedonia). Nekovarova et al. (2014) propose the co-ordination of "these two axes can create a mental representation of the human mind that can be focused outwards or inwards forming four domains," p.172.

An alternative, although compatible suggestion is that perceptual problems in schizophrenia (as discussed above) could contribute to deficits in empathy and theory of mind, for example, by impairing the interpretation of facial expressions.

From the foregoing, it might be predicted that negative symptomatology might be associated with a reluctance to respond, so this could be reflected in positive correlations with slower reaction times and a greater level of omission errors. Also, perhaps, a negative correlation with false positive responses - although unexpected in this data set since 50% false positive responses were made 3 individuals. Negative symptoms might also confer some resistance to distraction unless the distractor is of personal or emotional nature.

1.11 Summary of the Introduction

Considerable progress has been made concerning the identification of brain areas and pathophysiological processes associated with schizophrenia. Some evidence is substantive, for example, concerning pathophysiological cascades associated with NMDAR hypofunction states and the particular vulnerability of white matter to excitatory and oxidative damage. Other aspects may have less support in the form of replication or convergence but have been demonstrated in the laboratory and delineated in clear and exquisite detail, for example, the conditions under which long-term potentiation and long-term depression may occur. Yet in other areas, neural processes and the associated anatomical substrates may be poorly understood, for example, the function of the claustrum or aspects of processing within the striatal-thalamo-cortical loops. Consequently, the introduction has sought to take an integrative approach towards pertinent evidence and provide a context for the discussion of TRS.

TRS appears to be a distinctive category representing around 21-23% of individuals with a diagnosis of schizophrenia. This is distinguished clinically by the persistence of negative and cognitive symptoms and also biologically with a younger age of onset, no sex difference in prevalence and an absence of elevations in the presynaptic synthetic capacity for striatal dopamine which characterises FLRS individuals. It appears to be present at the first episode in about 84% of individuals, however, around 30% respond to conventional antipsychotic treatment initially but not subsequently, possibly due to an upregulation in D2 receptors in response to conventional antipsychotic medication and the development of dopamine supersensitivity.

Predictors of TRS appear to include a higher level of negative symptoms and a longer duration of untreated psychosis in the prodrome. However, one longitudinal study over a 10-year period observed deterioration in working memory digit span in a subgroup who had experienced psychosis over a longer period after diagnosis. Indeed, concerns have been raised that acute psychosis might be neurotoxic whereas there could be a lesser risk during the prodrome which has been the focus of research into DUP and has produced mixed observations.

The literature concerning TRS has suffered from a dearth of research and the lack of a consistently used definition. Recent reviews of the neuroimaging evidence did not identify an fMRI BOLD study comparable to the one here, and the diversity of studies on TRS may have contributed to a near-absence of replicated findings of any substance. However, some excellent PET and 1H-MRS studies on TRS have been conducted and there are, by now, some well-developed theories which may be compatible with this emerging evidence, both with respect to symptoms and possible neurobiological substrates. The introduction reviewed the major theories of schizophrenia and posed a question that has been asked by others (for example, Egerton et al., 2012; Gillespie et al., 2017)[31] as to whether a glutamatergic hypothesis might be more appropriate for TRS? Glutamatergic dysfunction, for example, caused by NMDAR antagonists, can precipitate or reinstate the symptoms of psychosis along with cognitive symptoms similar to those observed in schizophrenia. Also, decrements in GABAergic interneurons (or GABA synthesising enzymes), consequent upon glutamate of excitotoxicity could result in the loss of tonic inhibition in excitatory networks and lead to further glutamate excitotoxicity with diverse impacts upon symptoms and cognitive function.

The glutamate and GABAergic theories are therefore closely related and different aspects could gain prominence during the course of disease. One well-founded theory proposes primary pathology may lie in the hippocampus consequent upon decrements in a certain class of GABAergic interneuron (PVIs), possibly starting with hypofunction at the NMDARs they bear. This leads to hyperactivity in the dopamine cells of the VTA downstream which projects to the striatum (Grace, 2012; 2016). However, as outlined in the seminal hypothesis of NMDAR hypofunction, losses may occur in other brain areas as

[31] Egerton et al. (2012) raised the possibility that "clinical status following antipsychotic treatment in schizophrenia is linked to glutamate dysfunction." Similarly, Gillespie et al. (2017), concluded: "treatment-resistant schizophrenia appears to be characterised by a relatively normal dopamine system but an abnormal glutamate system, and significant decreases in grey matter," p.10.

PVIs are highly numerous and widely distributed along with the glutamatergic pyramidal neurons which they innervate (Goldman-Rakic et al., 1989; also see Stone et al., 2010).

Moreover, a substantive body of preclinical evidence indicates how a selective loss of GABAergic parvalbumin containing interneurons in schizophrenia might arise. This has been demonstrated in rodent studies involving maternal stress, maternal immune activation and redox dysregulation. Also, white matter appears to be particularly susceptible to excitotoxic and oxidative damage, but neuronal atrophy or loss is also possible. Indeed, Gillespie et al. (2017) observed significant decrements in grey matter volumes relative to controls and treatment responsive-schizophrenia may be specific to TRS and U-TRS, noting the alternative position of Mouchlianitis et al. (2016, b) that the reductions may be along a continuum reflecting illness severity. It is suggested here that reductions in PVIs could contribute to such decrements, as they may also bear NMDARs which may be particularly susceptible to damage when they have a greater preponderance of the NR2B subunit because these confer slow ion channel kinetics which allow more calcium ions to enter, increasing a cell's excitability at the risk of excitotoxicity and cell loss. (Further, not only are synaptic connections are "pruned" and reorganised during adolescence, but NR2B subunits on NMDARs may be substituted by other kinds). Interestingly, as commented in section 1.7.1, Ahmed et al. (2015) observed progressive reductions in grey matter during the first 6-9 months after commencing clozapine, inferring that grey matter loss might not necessarily be pathological as symptoms remitted and could, perhaps, reflect the pruning of aberrant connections. Moreover, lesser decrements in the left medial prefrontal and right middle temporal cortices were associated with a greater likelihood of treatment response.

Recent evidence suggests GABAergic deficits may compromise the ability to generate oscillations in the gamma range through reverberating microcircuits. This is an emerging area of science and the detection of GABA levels is still at the limits of what is technically possible but may prove to be important, for example, in one study working memory performance in healthy participants was observed to correlate positively with GABA levels in the DLPFC. Moreover, in another study by the same team, a 10% reduction in GABA was observed in the visual cortex of medicated PSZ relative to healthy controls. When observations were combined there was a strong correlation between GABA levels and a visual test of cortical inhibition (measured by orientation-specific, surround suppression) but not contrast sensitivity per se. This might have implications for selective attention certainly from a "bottom up" perspective where GABA may have a role in suppressing irrelevant activity, potentially affecting the specificity of encoding or signal to noise ratio. Some evidence indicates clozapine may reverse sensory gating deficits. It was also suggested

here, clozapine may help to compensate for the loss of PVIs through its high binding affinity for D4 receptors which are found at high density in the PFC, ACC and hippocampus, as discussed in section 1. 5. 6.

Towards the end of the introduction potential associations between hyperactivity in the DMN and negative symptoms were explored since it was proposed that negative symptoms might be associated with introspection and DMN activity which, in turn, my interfere with the performance of cognitive tasks. However, it was the evidence from preclinical studies on NMDAR hypofunction conducted by Olney and colleagues (1999, 1995) which highlighted the potential vulnerability of medial areas, including the anterior and posterior cingulate, which in humans are strongly associated with the DMN that helped to inform the second hypothesis of this study.

1.12 Aims and Hypotheses

As TRS has been under-researched and there were no comparable fMRI studies, this study was largely exploratory and intended as a preliminary characterization of the neurobiology of TRS. The primary aim of this research was to characterize TRS through clinical assessment, neuropsychological tests and an exploration of task evoked changes in the blood-oxygen-level-dependent (BOLD) signal at different levels of cognitive load during a verbal n-back working memory task, using functional magnetic resonance imaging along with the exploration of the association between the BOLD signal and clinical correlates.
It was hypothesised that:

a) TRS individuals would show attenuated engagement of an "executive" fronto-parietal network during working memory processing compared to controls.
b) Brain areas exhibiting altered haemodynamic response would include the cingulate gyrus and would be associated with task performance and symptom severity.

Secondary aims included the exploration of the association between clinical and cognitive variables and between the BOLD signal, clinical and cognitive outcome measures.

Chapter II - Methods

2.1 **Participants**

Participants for this study were recruited from within the catchment area of the South London and Maudsley NHS Foundation Trust (SLaM) and neighbouring area of Oxleas which is slightly less urban and more prosperous. All clinical participants had a confirmed diagnosis of schizophrenia or schizo-affective disorder and met modified criteria for TRS (based on those used in Kane et al., 1988) as they had been treated with at least two chemically different antipsychotics, at an adequate dose and for sufficient duration (of at least six months) but had not clinically responded before a trial of clozapine was tried.

A group of healthy control participants was also recruited, usually at short notice as "stand-ins" for scanning appointments that could not be filled by TRS participants. It was therefore not possible to carefully match the characteristics of this group with the TRS group with respect to social and demographic characteristics which are shown in Table 3. 1.

2.2 **Description of Recruitment Procedure**

Several people, helped with the recruitment of TRS participants during visits to clozapine clinics which are run for the purposes of regular monitoring for the risk of agranulocytosis, titration of clozapine and the dispensing of medicine and advice. Attendees who expressed an interest in the study were provided with a Participant Information Sheet which outlined the purpose of the study and what it entailed. They were encouraged to make an appointment, or 'phone to discuss aspects of research.

Written informed consent was required to take part in the study and permitting access to medical records and for radiographers to contact a participant's GP if necessary. Consent was also sought for neuroimaging data to be used in other studies. Where participants were willing to provide blood for genetic research, consent was again sought, but it was made clear this was not a requirement for participation in the neuroimaging study. Copies of the participant information sheet and consent forms are supplied in Appendix 7.

2.2.1 Screening and Exclusions

Neurological trauma, psychiatric co-morbidity (including drug addiction) and left-handedness[32] were exclusion criteria, along with other conditions that might interfere with the ability to perform the experiment task: for example, claustrophobia, glaucoma and finger stiffness (a possible legacy of treatment with conventional antipsychotics) which was tested by tapping out sequences with the right hand. For control participants, a personal or family history of any major psychiatric disorder were further exclusion criteria, if known.

An unforeseen de facto exclusion was body size, as weight gain is a common side-effect of antipsychotic medication and many individuals appeared too large to be comfortable within the narrow space of the fMRI scanner and so were not generally approached. MRI safety questions and medical checks to assess suitability were also conducted.

A diagnosis of TRS was confirmed by reference to medical records by the clinical consultant nurse, Tracey Collier.

2.3 Ethical Approval

Ethical approval was provided by Wandsworth (REC 09/H0803/81). The study was conducted in accordance with the World Medical Association Declaration of Helsinki and subsequent amendments (World-Medical-Association, 1965, 1996, 2008, 2013).

2.4 The Design of this Study and Procedure

The study was of cross-sectional design. All participants performed a verbal n-back task for the fMRI study, which also provided behavioural data. However, individuals in the control group did not participate in other aspects of the study, including neuropsychological assessments as they were recruited under a different protocol as part of a BRC "cluster study".

TRS individuals took part in a clinical interview on the day of the scanning appointment, whereas the collection of demographic information and neuropsychological testing was usually conducted at least a couple of weeks before to minimise fatigue. A further difference was that TRS participants had practice and familiarisation with the n-back task during the preliminary visit, partly to ensure they could perform the task and to minimise

[32] The Annett Handedness Questions were asked if there was any doubt (Annett 1970).

stress during the scan. This may have conferred an advantage relative to the control group but the practice sequence differed from that in the study.

2.5 **Social and Demographic Questions**

Relatively few questions were asked to minimise demands made upon participants (questions relating to socioeconomic status were dropped at the first interview after the participant appeared distressed; also, it was not part of the protocol to collect this information from the control group (2.4 above), similarly for years of education and other social and demographic aspects.

Some information was also obtained from medical records, for example, the duration of time between first diagnosis and receiving a trial of clozapine, and how many years had elapsed since the first episode. As illicit drugs, as well as smoking nicotine, are known to affect the same neural circuitry implicated in schizophrenia (e.g. Steeds et al., 2015; Moran et al., 2018), TRS participants were asked whether they had ever tried a particular drug (from a list) and, if so, whether they could remember how old they were at the time. It was emphasised there was no need to answer the questions, however, participants seemed generally forthcoming and perhaps, "first ever" experiences tend to be recalled more easily even though the chronology might be doubted[33]. The information was subsequently related to the age of the first psychiatric admission for psychosis obtained from clinical records. Information about subsequent or current drug use (apart from nicotine) was not sought. Social and demographic data is presented in Section 3.1.1 and Appendix 1.

2.6 **Clinical Assessment**

This involved a semi-structured interview by a trained interviewer using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). The PANSS interviews were conducted by clinical nurse consultant Tracy Collier. Also, at least one interview was conducted under her supervision by master's student James Hurley and, another, by Dr. James Gilleen.[34] It was considered unnecessary to evaluate inter-rater reliability.

[33] There may not be a "classic paper" on primacy effects in long-term memory, possibly, because these might be difficult to verify. However, by definition, "first ever" experiences should be less susceptible to proactive interference from similar representations. Moreover, they may be more likely to be remembered because of their novelty and the co-release of dopamine (the "learning signal" described by Abi-Dargham, 2017). Further, drug-taking may have enhanced this by stimulating processes associated with reward.

[34] The subscale scores for this participant, whose total score was in the middle of the group's distribution, are not included in the analyses.

The development of the PANSS scale and analysis of its factors are referred to in section 1.3 of the introduction. Clinically, it is useful because it has been widely used and considers a broad range of symptoms and provides a global measure of symptom severity which is useful for comparisons across studies. There is no predetermined script and questions addressing the items (listed in Table 2. 1), can be raised in any order, thereby providing useful flexibility during interview. Each item is rated on a scale from 1 to 7, corresponding to: absent, minimal, mild, moderate, moderate-severe, severe or extreme. The minimum score is 30 (as the scale comprises 16 items in the General Scale and 7 items in each of the Positive and Negative Scale). However, the PANSS is not a continuous scale as the items are qualitatively different.

Table 2. 1 List of Items in the Positive and Negative Syndrome Scale (PANSS)

Positive Scale	**General Scale**
P1 Delusions	G1 Somatic concern
P2 Conceptual disorganisation	G2 Anxiety
P3 Hallucinatory behaviour	G3 Guilt feelings
P4 Excitement	G4 Tension
P5 Grandiosity	G5 Mannerisms & posturing
P6 Suspiciousness/persecution	G6 Depression
P7 Hostility	G7 Motor retardation
Negative Scale	G8 Uncooperativeness
N1 Blunted affect	G9 Unusual thought content
N2 Emotional withdrawal	G10 Disorientation
N3 Poor rapport	G11 Poor attention
N4 Passive/apathetic social withdrawal	G12 Lack of judgement & insight
N5 Difficulty in abstract thinking	G13 Disturbance of volition
N6 Lack of spontaneity &	G14 Poor impulse control
flow of conversation	G15 Preoccupation
N7 Stereotyped thinking	G16 Active social avoidance

2.6.1 Analysis of the Clinical Data and Creation of Symptom Groups

As indicated in the introduction, the classification of symptoms remains an active area of research and debate. Items on the general scale usually disappear or are reassigned to other dimensions in factor analyses so correlations were not conducted with the general scale in this study. Also, a third of the items on the PANSS disappeared in Wallwork et al.'s (2012) confirmatory factor analysis which might cast doubt on usefulness of individual items, also given the relatively small number of TRS participants in this study, analyses were not conducted with individual items. Further, the diversity of symptom profiles across patients presents another issue for schizophrenia research, as Howes et al. (2017) observe "It may not be appropriate to compare groups of patients in whom the illness is predominantly resistant in another domain." p.219 (Treatment-Resistant Schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group Consensus Guidelines on Diagnosis and Terminology).

It was therefore decided to focus on overall symptom severity so various analyses are presented where the TRS participants have been divided into two groups (referred to as Lower PANSS and Higher PANSS) according to their level of symptoms. The term "Higher" is preferred to "High" as the latter might imply a greater level of symptoms than generally indicated by the scores. A median split of the distribution of total scores was not possible as three participants had identical scores in the middle of the distribution, however, it was possible to achieve two groups with a minimum of 6 points of separation between them by assigning 14 participants to the lower PANSS group and 12 to the higher PANSS, with median total scores of 41 and 66 respectively[35].

2.7 Neuropsychological Assessment

2.7.1 The Wechsler Abbreviated Scale of Intelligence (WASI)

Intellectual aptitude was assessed using the Wechsler Abbreviated Scale of Intelligence (WASI) which provides estimates that correlate highly with the more extensive Wechsler Adult Intelligence Scale (WAIS-III) Full-scale Intelligence Quotient which has been standardised in the general population and enables scores to be adjusted for age and gender. The two subscales of performance IQ (PIQ) and verbal IQ (VIQ) reflect two factors which equate to "fluid" and "crystallised" intelligence (Cattell 1963) and have strong coefficients of congruence "suggesting factorial equivalence across the standardization and clinical

[35] The minimum gap between the groups widened to 9 points in some analyses when one participant (ID32), who had a total PANSS score was not included as scores on the Negative and Positive scales were unavailable. Perhaps, serendipitously, their total score was in the middle of the distribution and this was the only assessment not conducted or supervised by TC.

samples" (Ryan et al., 2003). The WASI comprises four tests: two addressing performance (Block Design and Matrix Reasoning) and two for verbal aptitude (Similarities and Vocabulary). The results from these are combined to produce an estimated Full-Scale Intelligence Quotient (FIQ). In this study, the scores were adjusted for age and gender; percentiles were also obtained for comparisons with population norms and those on the test battery. However, standard IQ scores are expressed elsewhere because these are normally used in the literature (also, to avoid confusion, for example, the t-score at the 50th percentile is 50, whereas for the standard score IQ scores it is 100).

Further investigations were conducted concerning an unexpected asymmetry between the WASI subscales for some individuals (illustrated in the results at Figure 3. 2). This was fairly sizeable, exceeding 10 points in 52% of the participants, with the majority showing an imbalance which favoured performance IQ (PIQ). Whereas verbal IQ (VIQ) scores were superior only in a small group of 4 participants. Apart from potentially being an interesting observation in its own right, the presence of these sub-groups could present a confound in the data. Therefore, further descriptive and exploratory correlational analyses were conducted concerning the groupings of "superior PIQ" (PIQ>VIQ), "no asymmetry" and "superior VIQ" (VIQ>PIQ), in order to assist the interpretation of results.

A descriptive characterisation of the VIQ>PIQ individuals is presented in Table 3. 19 (also Appendix 5) and appeared so distinctive that some analyses were repeated in a reduced set of 20 TRS participants which excluded their scores. These concerned correlations involving negative symptoms and variables associated with attention (Table 3. 17: 0-Back SDs, CPT-IP scores and percentage of omission errors in the n-back task); also, between all these with estimates of IQ (Table 3. 18). All these correlations in the reduced set are reported in Appendix 5: Table Appx. 5. 1 and Table Appx 5. 2

2.7.2 The MATRICS Consensus Cognitive Battery (MCCB)

The MCCB arose from a U.S. funded collaborative project at five academic sites: "the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS)" and has been standardised and validated with 300 community residents and 176 individuals with schizophrenia or schizoaffective disorder (Green, Harris, and Nuechterlein 2014; Kern et al., 2011). Specifically developed for schizophrenia research and drug trials, it was recently described as "the gold standard" (Lees et al., 2015). Many of its tests are well-established and were selected by consensus from more than 90 tests in a process that considered test-retest reliability, usefulness regarding functional outcomes,

tolerability and practicality (Nuechterlein et al., 2008; Kern et al., 2011). A computer was necessary for scoring overall composite scores and for administering the Continuous Performance Task - Identical Pairs (CPT-IP), however, a traditional "paper and pencil" approach with a stopwatch was used for other aspects of administration and data collection.

Seven separable domains of function were identified during the MCCB process, which are summarised in Table 2. 2 along with the ten tests chosen to assess them and a brief description of testing procedures. These concerned aspects of executive function, working memory, verbal fluency, measures of verbal learning and memory, visual learning and memory, processing speed, sensorimotor aspects, attention and emotional understanding/social cognition (Nuechterlein et al., 2004).

The MCCB generated a number of variables for exploratory analysis, including comparisons between lower and higher PANSS groups. Correlations have been observed between different domains and intelligence scores (e.g. August et al., 2012; Mohn et al., 2014), therefore in summary charts of the WASI and MCCB results in sections 3.2 and 3.4 scores are also expressed as percentiles as these are readily comprehensible in relation to population norms from standardisation studies (Crawford, 2003).

As this study lacked a FLRS group for comparison, the T-scores for the domains in this study are displayed alongside others from published studies (Table Appx. 4. 8, Figure Appx. 4. 1). However, in order to evaluate heterogeneity amongst the MCCB tests in this study a series of within-participant comparisons were conducted using the Wilcoxon Signed Rank Test with scores on category fluency (animal name generation) which had the best performance at the 38th percentile. Uniquely, the scores were virtually identical for lower and higher PANSS groups thereby strengthening the case for its suitability as a baseline. These are reported in section 3.4.1, Table 3. 8.

Further, as the processes that underlie verbal and visual learning may largely differ from the executive processes of verbal and visual working memory, some exploratory correlations were conducted between these and variables assumed to reflect higher cognition and executive processes: the WASI subscales and MCCB overall composite scores (Table 3. 9).

Table 2. 2 MCCB Tests and Domains

Cognitive domain	MCCB test	Dependent Variable
Speed of Processing	Trail Making Test, part A (TMT - A).	Time taken to draw a line connecting 25 circles according to numeric order indicated by labels.
	Brief Assessment of Cognition in Schizophrenia (BACS) Symbol Coding. (A digit symbol substitution test)	Total number of correct pairings within 90 seconds.
	Category Fluency (A verbal fluency test similar to one used by Brenda Milner (1964).	The number of animal names generated in 60 seconds.
Verbal Learning	The Hopkins Verbal Learning Test - Revised™ (HVLT-R™)	Total number of words correctly recalled from a 12-item list presented 3 times.
Visual Learning	The Brief Visuospatial Memory Test-Revised™ (BVMT-R™)	Recall and reproduction of six 2-dimensional abstract figures (with geometric elements) presented together for 10 seconds, repeated 3 times.
Working Memory	Wechsler Memory Scale (WMS-III) Spatial Span. (Similar to "Corsi Blocks")	Total number of correct reproductions of tapped sequences (forward and backwards), presented at increasing length.
	Letter-Number Span (LNS) (University of Maryland)	Number of letter-number sequences correctly re-ordered (numbers first, then letters) which progressively lengthen.
Reasoning and Problem Solving	The Neuropsychological Assessment Battery (NABs): Mazes	Total score based on time to complete seven mazes of increasing complexity.
Social Cognition	Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT): Managing Emotions	Scoring determined by a consensus method about "the effectiveness of solutions about regulating emotions in oneself and interactions with others" (Kern et al., 2011).
Attention/Vigilance	Continuous Performance Task - Identical Pairs (CPT-IP)	Mean d-prime values for 2-, 3-, and 4-digit conditions

Exploratory correlations were also conducted between selected variables and the duration of treatment with clozapine and also, the elapse of time from diagnosis until treatment with clozapine since, as Table 3. 3 shows, the lower PANSS group had received it for a median of 9.5 years, a significantly longer duration than in the higher PANSS group where the median duration of treatment was 4.5 years. Individuals in the lower PANSS had also started a trial of clozapine a median 4 years after their initial diagnosis (assumed to be the

FEP), compared with 7 years in the higher PANSS group (a difference which, arguably, had "trend significance).

The variables for correlation were chosen on the basis they appeared to distinguish four participants with an intellectual asymmetry that favoured VIQ (Table 3. 19 and Appendix 5) and who had waited to receive clozapine for a mean average of 2.5 years, compared to 6.6 years for the group as a whole (Table 3. 3). These concerned total PANSS score, the number of negative symptoms, 0-Back SDs and 0-Back RTs, WASI estimates and the percentage of omission errors to targets in the n-back study, category fluency and sustained attention/vigilance scores and the MCCB Overall Composite. Verbal learning (HVLT-R) and total free recall on the first trial of the HVLT-R were also selected in the light of an observation on recency (below). A corresponding correlation was conducted with visual learning (BVMT). These correlations are reported in Table Appx. 4. 7 (a, b).

The possibility that visual and verbal learning might deteriorate during the time between diagnosis and a trial of clozapine led to a further decision to conduct partial correlations with age as a covariable. The time between first episode/diagnosis and receiving a trial of clozapine was slightly positively skewed (skewness = 1.007, standard error = .464, with a kurtosis of .640) and had initially been treated as non-parametrically distributed variable, however, this marginal decision was revised as partial correlation was only available for parametrically distributed variables in SPSS (these are reported at the end of section 3.4.3).

An unplanned analysis was also conducted with data from one of the MCCB tests. This concerned free recall on the first trial the HVLT-R. This was done because the 12-item list is presented auditorily and requires immediate recall, yet few participants appeared to demonstrate recency[36] by recalling the most recently presented items first, notwithstanding, clear instructions that the words could be recalled in any order[37]. This seemed surprising as individuals might be expected to seize upon the last two or three items held in a transient auditory store after the presentation of a long list that is likely to exceed their short-term memory span. The results are presented in section 3.5.

[36] The recency effect reflects a common strategy that appears to take advantage of items held in a limited capacity, transient, auditory store. Noted by Hermann Ebbinghaus in the 19th century (Baddeley, 1976).

[37] "I am going to read a list of words to you. Listen carefully, because when I'm through, I'd like you to tell me as many of the words as you can remember. You can tell them to me in any order. Are you ready?"

2.8 Magnetic Resonance Imaging

2.8.1 Equipment and Image Acquisition Parameters

Functional and structural MRI data were collected at the Centre for Neuroimaging Sciences, King's College London using a Signa HDx 3.0 Tesla MR scanner (GE Medical Systems, Milwaukee, WI, USA), with an 8-channel head-coil.

2.8.2 Functional MRI parameters:

One hundred and eighty-six T2*-weighted images depicting the BOLD contrast during the n-back were acquired in the axial plane, parallel to the anterior commissure–posterior commissure (AC–PC) line using echoplanar imaging. The parameters are described in Table 2. 3

Table 2. 3 fMRI Image Acquisition Parameters for the Verbal N-Back Task

Number of slices:	39
Slice thickness (mm)	3.5
Inter-slice gap (mm)	4
Number of functional images	186
Echo time (TE) (ms)	30
Repetition time (TR) (ms)	2000
Flip angle (degrees)	75
Matrix size	64 x 64
Pulse Sequence	epiRT
Field of View (FOV) (cm)	24 x 24
Scan time (seconds)	372

2.8.3 Structural MRI parameters:

To enable accurate normalisation of the images for individuals into standard stereotactic space (prior to mapping on to the Talairach template), high resolution GE-EPI whole brain volumes were acquired with axial slices parallel to the plane of the AC-PC line: TE=40ms, TR = 3000ms, excitation flip angle 90 degrees, number of slices 43, thickness/gap 3.0/0.3, matrix 128 x128, field of view 24cm x 24cm.

2.9 The Experimental Paradigm: A Verbal N-Back Task

The n-back task in various forms (visuospatial and verbal), has been widely used in neuroimaging as a task of working memory and executive function. It was used for the neuroimaging part of this study while on-line recording of responses also generated behavioural data which could be useful in the characterisation of performance by participant groups and, perhaps, providing some convergent support for neuropsychological assessment which generally occurred on different days.[38]

The verbal n-back task involves holding in memory a temporary sequence of items (usually 1 to 3) and updating them as the list of to-be-remembered items progresses. Responses are made when a stimulus reoccurs at the designated position in the sequence, e.g. upon immediate repetition (1-Back), after another stimulus has intervened (2-Back) or after two stimuli have intervened (3-Back). This last condition represents the highest level of task difficulty/cognitive load and is frequently omitted in studies with clinical participants.

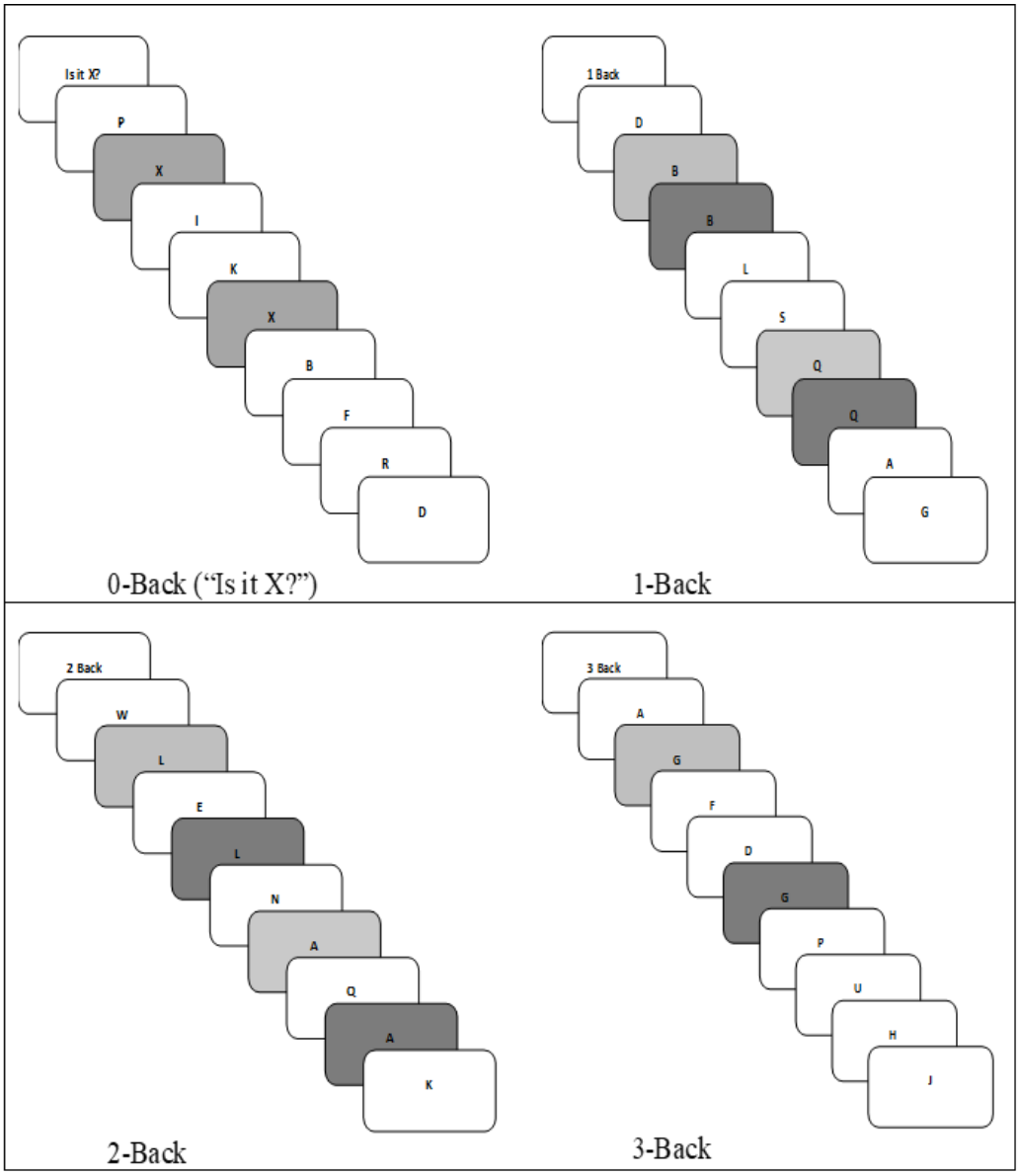
The baseline condition (0-Back) is assumed to evoke the same haemodynamic responses apart from those relating to aspects of working memory itself, thereby, providing the substrate against which changes in the haemodynamic response are compared. The "verbal 0-Back" used here, required a button to be pressed with the right index finger when the letter "X" appeared. Overall, the n-back task requires sustained attention along with the ability to remember items stored temporarily and, presumably, the ability to inhibit "activated" representations or, at least ignore them through selective attention as new stimuli take their place (part of the updating function). It is also necessary to apply task rules and demonstrate flexibility to cope with changing task demands between blocks. Successful performance, therefore, requires a considerable amount of attention, continuous monitoring, also, the inhibition of erroneous prepotent responses.

A short practice session on the n-back task was given off-line to all participants during the hour before their scan, when they were further assessed for safety by the radiographer. Once settled in the scanner, participants lay supine and wore ear-phones to partially shield the noise from the scanner and to enable communication with the experimenter and the radiographers. A panic button was held in the left hand, and the button pad for the response in the right (usually resting upon the thigh). Visual stimuli were projected onto a large screen at the foot of the trolley where participants lay and were clearly visible from inside the borehole of the scanner via a two-mirror system.

[38] Only two participants completed all assessments on the day of scan and clinical interview.

At the start of the experiment, instructions were read aloud by the experimenter while a fixation cross was displayed on the screen. These included a request that the participant should keep their heads as still as possible and not to talk out loud. The different levels of the task were described and participants were requested to press the button in their right hand whenever they saw the target letter. (However, this cannot be described as a speeded reaction time paradigm as they were not asked to respond "as quickly as possible"). There were 3 experimental blocks for each condition, presented in a pseudo-random order that was held constant for all participants. Each block comprised 14 trials of individual letters, including 3 targets. Response latencies, correct responses and errors were recorded on-line. A partial sequence is supplied in Figure 2. 1 below for illustrative purposes.

Figure 2. 1 Illustration of partial sequences in the Verbal N-Back Paradigm



Shown from back to front: each experimental block started with an instruction denoting the condition. The first appearance of a target in the 1, 2 and 3-back conditions is highlighted in this figure in pale grey, with repeated occurrences requiring a response in dark grey (highlighting for illustrative purposes only).

2.10 Behavioural Variables from the N-Back Task

Reaction times (RTs) for correct responses to target letters, omission errors and false positive responses, also standard deviations (SDs) at different levels of cognitive load offer an array of potentially interesting variables. However, as many processes are likely to contribute to these measures, the simplicity and ease of the 0-Back condition (as evidenced by faster reaction times and excellent accuracy), offered the best prospect of providing useful variables, with the exception of error data where the frequencies were too low. Further, it was hoped that the simple measures of mean RTs and SDs in the baseline task by individual participants might, to some extent, capture "state" or possibly "trait-like" characteristics prevailing around the time of scan

2.10.1 Error Data

In every experimental block there was an opportunity to make 3 omission errors to the target and 11 omission errors (amounting to 9 target errors and 33 omission errors in each condition and 36 target errors and 132 omission errors across the experiment as a whole). It is proposed omission errors could provide an index of sustained attention as they may occur during lapses in attention. As discussed in the introduction, it is further proposed attentional lapses might be mediated by negative symptoms such as apathy or anergia, or even be related to hyperactivity in the DMN acting as a "pull factor" which constantly draws attention back to the inner world.

By contrast, false positives might reflect the influence of entirely different factors, for example, decision-making in the presence of insufficient, or degraded information. There is, for example, a literature with several theories (described in Rausch et al., 2016) on "jumping to conclusions" in schizophrenia - a robust phenomenon where individuals make probabilistic judgments prematurely on the basis of limited information while appearing confident about their responses. One explanation, might extend to failures of inhibition of prepotent motor responses, possibly fuelled by an elevated dopaminergic state which confers aberrant salience. This generates a prediction that false positive errors might correlate with positive symptoms. However, irrespective of whether it is possible to progress these questions within the scope of this study, error rates offer an interesting source of data providing different kinds are analysed separately.

2.10.2 Standard Deviations as a Proxy Measure of Attention

In Miller and Cohen's (2001) influential "theory of prefrontal cortex function" top-down attentional control is required in situations demanding flexibility in responding, for example, in the context of changing task demands, or in response to the detection of performance errors (Carter and van Veen, 2007). As a result, it is proposed mean standard deviations in the 0-Back task could provide a simple measure of the ability to sustain attention under cognitive control. Also, the 0-Back task (pressing a button every time an "X" appears) resembles the first continuous performance task (CPT) by Rosvold et al. (1956), which was designed to assess "attention or alertness" and was subsequently adopted to measure sustained attention in classic tasks like the Conner's CPT-3. These will be more extensive than the 0-Back task and parameters such the presentation rate, the number of trials and proportion of targets are manipulated, however, there is some face validity in proposing this behavioural data might provide a measure of sustained attention.

The Conner's CPT paradigm has been demonstrated in healthy participants to activate a network that is similarly activated in other studies of sustained attention, for example, Tana et al. (2010) observed activity in a large-scale network that involved the frontal, temporal, insular and occipital cortices and cerebellum with the greatest activation observed in the right ACC. This appears to be consistent with the engagement of the central executive and salience networks as described by Menon and Uddin (2010). The Continuous Performance Task - Identical Pairs is included in the MCCB, however, this is more perceptually demanding as the stimuli (comprising 2,3 or 4 digits) are presented at a relatively fast rate of 1 per second for long blocks and participants are required to respond if the stimulus on the current trial matches the previous one, which may be perceptually similar. As Rapisarda et al. (2014) observe "subjects need to decode each stimulus carefully and keep it in working memory until it can be compared with the one immediately following." (p.234) Lopez-Luengo et al. (2016) suggest the literature on the CPT is divergent because "more difficult CPTs can place additional processing demands on the subject."

The creators of the MCCB will have been well aware of such issues, for example, Nuechterlein et al. (2015) describe the CPT-IP as involving "sustained attention in a situation demanding working memory." (p.5) However, it has good test-retest reliability and attention, as measured on this test, "is a reliable, stable trait that reflects a biological stability to schizophrenia" (Cornblatt and Malhotra, 2001, p.14). Nuechterlein et al. (2015) have since compared performance on the CPT-IP with the degraded stimulus version

(DS-CPT) where the digits are blurred, at five different sites with a sample of 972 healthy controls and 1140 participants with schizophrenia. No relationship was found between visual acuity and discrimination performance on the DS-CPT, and only a slight relationship with the CPT-IP, while worse performance on the both tasks was associated with poor cognitive function and fewer years in education. Moreover, only a weak relationship with negative symptoms was found, if at all, as levels varied across sites. Yet, while Nuechterlein et al.'s (2015) study did not specifically identify TRS or U-TRS individuals, those receiving a combination of atypical and typical antipsychotics exhibited significantly worse performance on the CPT-IP than while the decrement on the DS-CPT was described as showing "a similar but nonsignificant tendency".

As the CPT-IP was not tested on a TRS population, and the CPT-IP places demands on perception and working memory, a "purer" and simpler measure of sustained attention might help to provide convergent or supplementary evidence.

2.10.3 Reaction Times

As shown in Table 2. 2, the domain of processing speed is measured by the composite of three tests in the MCCB where response times are the end point of the integration of different sources of information and stages of processing, for example, involving perception and encoding, response selection and the inhibition of competing responses. Again, it is proposed RTs in the 0-Back condition might provide a simpler measure of processing speed than more complicated or demanding tasks, and perhaps convergent evidence if the MCCB measure is questioned in some way. Further, this measure might reflect "state"-like characteristics (including arousal and responding contingencies such as speed/error trade-offs) that may have prevailed for the duration of the experiment. (Table Appx. 4. 2 reports correlations between measures of speed and the MCCB overall composite).

While RTs and SDs are usually highly correlated and difficult to separate. SDs in the 0-back condition are proposed to provide a proxy measure of attention (defined for these purposes as reflecting aspects of attention that are largely accessible to conscious control - the ability to maintain attention and resist distraction, i.e. sustained attention and selective attention respectively). This proposition was tested in correlations between SDs in the 0-back condition and measures which might be associated with attention: Negative symptoms, Full-scale IQ, Performance on the CPT-IP task of the MCCB.

2.11 **Statistical Analysis of Non-Imaging Data**

The IBM SPSS Statistics software package was used to analyse neuropsychological and behavioural measures and to chart scatterplots. Fisher's exact test was used to determine if there was a significant difference between expected and observed frequencies for gender[39]. The parametric Pearson product moment correlation coefficient or non-parametric Spearman's rho were selected according to assumptions. Between-group comparisons used the independent-samples t-test for normally distributed variables, or the non-parametric Mann-Whitney U-test, again, according to assumptions. All comparisons were two-tailed. Significance levels were rounded up to p = .001 where SPSS stated p = .000, with the exception of Table Appx. 4. 2 concerning correlations involving MCCB domain and composite scores where there was a meaningful difference between p values at .001 and others specified as p = .000. The latter were labelled as p < .0005.

A decision to use, potentially less sensitive, non-parametric tests for comparisons involving continuous variables between the lower and higher PANSS symptom groups was made, even though skewness ranged from 0.501 to 0.661 for the majority of the variables, because the number of participants were judged too few (below 15); also, the shapes of the distributions often varied between lower and PANSS groups. This was a subjective decision that follows Saroj et al. (2016).[40] McDonald (2014) has observed "there don't seem to be any objective rules on how much non-normality is too much for a parametric test." (pp 133-136 on "non-normality"). Even, for larger groups in the behavioural data, it was necessary to be circumspect where, for example, the Kolmogorov-Smirnov Test of Normality confirmed there was heterogeneity in the distributions across the different experimental conditions of both controls and TRS participants (Table 3. 11).

It is further noted partial regression for non-parametric data is not available in SPSS and regression with small datasets is inadvisable so these techniques were not used in exploratory analyses of asymmetries between the WASI subscales.

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[39] The chi-square test for independence (χ^2) was not used as the expected frequency of female participants in some cells was too low.

[40] "Nonparametric tests make no or very minimal assumptions about the probability density from which the data are derived. They are used when the sample size is small, when the data are not normally distributed and cannot be approximated as normal, and when using non numerical (rank, categorical) data. The nonparametric tests are often a good option for small sample sizes (n < 30)." (Saroj, et al., 2016, p.79).

The on-line behavioural data (RTs) was screened twice for outliers, once using a cut-off of 3 standard deviations above the mean for each condition in each group, which resulted in no exclusions and again using a limit of 2.5 SDs above the mean. As variability in responding is of interest and there was a need to conserve data (the experiment provided a maximum of 9 correct responses to target stimuli per participant in each condition), a screening limit of 3 standard deviations was chosen except where stated. This may have had minimal effect as only 5 scores in the control group (0.66% of correct response) and 2 in the TRS group (0.21% of correct responses) fell within this band.

2.11.1 Multiple Comparisons

The nature of this study was largely exploratory given the dearth of evidence on TRS, and the collection of clinical, cognitive and behavioural measures leads to an accumulation of variables. This raises the problem of multiple comparisons because it increases the likelihood of Type I Error, i.e. deeming a finding is significant when it is not. However, a common criticism of correction techniques which adjust the alpha level is that they are overly strict and undermine power. This may lead to the neglect of potentially useful observations and even publication bias (Nakagawa 2004). One way of circumventing this is to be highly selective but this stifles exploration and may also lead to "cherry picking" where significant results are more likely and, therefore, also risks bias. In any case, it may be remiss not to conduct some analyses when the data is available.

The approach taken in these analyses seeks to find a balance by applying a probability value of 0.05 as the significance level for all non-imaging tests and to look for convergent evidence upon interpretation. However, the revised alpha after Bonferroni correction, restricted to "families" of tests, is also provided for reference in some analyses.[41] The results of neuropsychological, clinical and behavioural comparisons are "unadjusted" unless otherwise stated. Following the recommendations of Nakagawa (2004), exact p-values are also reported[42], often with the effect size thereby, providing some indication of potential biological or practical importance. These are evaluated using Cohen's (1988) guidelines: for comparisons using the Mann-Whitney U test, r =.10, .30 and .50 indicate small, medium and large effect sizes respectively. (Similarly, for Eta-squared = .01, .06 and .14 in t-tests).

[41] Had the number of variables been more extensive, the "false discovery rate" might have been controlled instead.

[42] Except where p = .000 and is rounded up to .001.

Cohen (1988) also proposed the strength of a correlation coefficient is small if r = .10 to .29; medium if r = .3 to .49; large if r = .50 to 1.0.

A further reason to be cautious arises from the recognition that while neuropsychological assessment may be useful for descriptive purposes and comparing individual scores with standardised norms, large numbers of participants are usually required to establish the robustness of observations and inferences made at group level, even when individual studies report highly significant results. Apart from methodological and recruitment differences, other sources of variation include intra-individual factors including transient fluctuations in "state". The primary value of this rare dataset surely lies not in disproving hypotheses but in highlighting potential lines of enquiry and the generation of hypotheses.[43]

2.11.2 Correlations between Symptoms, Cognitive and Behavioural Variables

Section 3.7 presents some intercorrelations for the TRS group between clinical measures, neuropsychological assessments and behavioural measures from the n-back task. In particular it was proposed in the introduction that negative symptoms might interfere with or, in some other way, be associated with aspects of cognitive control and attention, so exploratory correlations were conducted between negative symptoms and measures proposed to be associated with attention (0-Back SDs, CPT-IP scores and the percentage of omission errors on the n-back task). However, both negative and positive symptom scores were generally low across the TRS group (n=26) with median scores of 14 and 11, respectively (were the minimum score is 7 and the maximum is 49 on both scales), which could reduce the likelihood of significant correlations. The results of correlations with negative symptoms are shown in Table 3. 17 below and depicted in Figures 3.11 and 3.12.

With the exception of omission errors in the n-back task, which was considered the weakest correlate, a second set of exploratory correlations were conducted involving these variables and estimated IQ scores. In addition, correlations were performed with a variable that indicated IQ asymmetry - the difference between individual scores on the WASI subscales. The results are shown in Table 3. 18 along with scatterplots (Figures 3.13, 3.14, 3.15, 3.16).

[43] Baddeley (2012) on Lakatos and Popper, p.4.

2.12 **Functional MRI Analysis Using XBAM**

The data were analysed using the XBAM (version 4.1) software, developed at King's College London, Institute of Psychiatry (Brammer et al., 1997), which uses a non-parametric approach based on permutation strategies which arose from a desire to minimize assumptions (Thirion et al., 2007). A history supplied with the program explains: "The first innovation in XBAM was not to assume normality but to use permutation testing to construct the null distribution used to make inference about the probability of an "activation" under the null hypothesis. The statistics used were also median rather than mean based to give more robustness against outlier effects. The second innovation was to recognise the existence of correlation in the residuals after fitting a statistical model to the data. If not taken into account, this inflates the type I error rate leading to an unacceptable level of false positives. The third innovation was the adoption of a two-level approach to data analysis in which the response sizes computed from the model fit for each individual (analogous to beta coefficients in SPM) were standardised with respect to their variances (residual noise) before embarking on the second, multi-subject, phase of analysis. This latter innovation effectively permits a mixed effects analysis of group level fMRI data by taking into account both intra and inter subject variances."

Further detail and validation can be found in Bullmore et al. (1996) and Brammer et al. (1997). Fusar-Poli et al. (2010), further demonstrated the sensitivity of XBAM methodology in a comparative study of techniques, for example, observing it detected the BOLD response in the insula, temporal lobe (including the middle and inferior temporal gyri) and putamen, whereas a parametric package could not[44]. Also, in Thirion et al. (2007), whose analysis involving "more than 80" subjects, compared the validity and implications of parametric assumptions compared with non-parametric ones. The most commonly used measure of response size (unstandardised beta) in fMRI analysis was observed to depart from normality in 22% of intracerebral voxels leading to the observation "Non-normality is very significant in wide regions of the brain." One of their conclusions was that "mixed effects tests are much more reliable than random effects tests." This also supported permutation-based inference and cluster, or parcel level, as opposed to voxel level inference - all of which are features of XBAM.

(For a full description and references see http://www.brainmap.it)

[44] This comparison involved XBAM version 3.4 and The Statistical Parametric Mapping (SPM) version 2.6.

XBAM was therefore chosen for its sensitivity as it enables the detection of small but highly activated clusters and, also, because the current study comprises a relatively small number of individuals (a minimum of 20 recommended by Thirion et al. (2007) for reliability in fMRI studies). Moreover, the problem of multiple comparisons is usually addressed through techniques such as the Bonferroni correction but, in classical fMRI approaches to voxel-by-voxel tests this is especially problematic and may lead to overly conservative corrections, reducing the detection of true differences. Indeed, optimal thresholds can be found which "are rather lower than usual corrected for multiple comparison thresholds" (Thirion et al., 2007). XBAM avoids the need for correction through the generation of null distributions which can be generated either through permutation sampling from all the voxels in the brain (global technique) or through local permutation at each voxel (Bullmore et al., 1999). The default (global) permutation was used in these analyses. In addition, cluster thresholds were adjusted to minimise the risk of type 1 error.

Age was used as a covariate in all the neuroimaging analyses as functional neuroimaging has demonstrated this to be an important biological variable where a sizeable a literature has demonstrated influences upon fMRI BOLD measurements (Heinzel et al., 2017; Rieckmann et al., 2017; Keller et al., 2015). Indeed, the TRS group was older than the control group (Table 3. 1).

However, IQ was not used as a covariate. Within a framework that regards schizophrenia as a neurodevelopment disorder (Murray et al., 2017), premorbid IQ score is strongly associated with risk for schizophrenia (Khandaker et al 2011). Therefore, IQ is confounded with and/or by schizophrenia in its different forms (e.g., TRS), and as it is intrinsic to schizophrenia it cannot be separated from its effects. On a methodological level, IQ in schizophrenia does not meet the following requirements for a covariate: (a) the assignment to the independent variable (e.g. schizophrenia) is done randomly; (b) the covariate is associated with the outcome measure, but this relation is not central to the research question; (c) the covariate is not related to the independent variable (Huitema, 1980). This is why the recommendation by Dennis et al. (2009) was followed and IQ was not controlled in the analyses of working memory performance.

2.12.1 Individual and Group Mapping

Before the images could be processed by XBAM software, they were converted from their original format (University of North Carolina, UNC format) to ANALYZE format (Mayo Foundation). This involved automated processing. The XBAM analysis is described below.

2.12.2 fMRI Pre-Processing

Data were processed to correct motion, intensity and spin excitation history (Bullmore et al., 1999) and were smoothed prior to statistical analysis and normalization, i.e. in native space. First, fMRI data were realigned in order to minimise movement artefacts (Bullmore et al., 2001) and smoothed using a Gaussian filter ("full width at half maximum" (FWHM) 8mm) to improve signal-to-noise ratio over each voxel.

2.12.3 IBAM module (Individual Brain Activation Mapping)

The next step involved within-subject analysis of data for individuals in native space where peak responses to the experimental paradigm were detected by fitting a model to the time series at each voxel, at each phase of the task (0-Back, 1-Back, 2-Back, 3-Back, specified in the time matrix of a model file) and convolved using Poisson functions (modelling responses at 4 s and 8 s, to provide an estimate which allows for variability in the haemodynamic delay). Then the "best fit between the weighted sum of these convolutions and the time series at each voxel was computed using the constrained BOLD effect model suggested by Friman et al (2003)".[45] This reduced the risk of physiologically unlikely results and enabled the further computation of a goodness of fit statistic at each voxel, the sum of squares ratio (SSQ), which is further described as of the ratio of the sum of squares of deviations from the mean image intensity (over the whole time series) due to the model to the sum of squares of deviations due to the residuals (SSQ ratio)"[34]. The null distribution against which any SSQ ratio can be compared for significance was then generated using the wavelet-based time series resampling method described in Bullmore et al. (2001) and then fitting the model to the resampled data. This enables the calculation of the SSQ ratio needed to threshold the statistical maps for any level of type 1 error rate (for example, SSQ ratio values in the observed data lying above the 99th percentile of the null distribution have a probability under the null hypothesis of $p < 0.01$). This permutation method has been shown to give excellent Type I error control and has been demonstrated for suitability with data acquired at 3 Tesla (Bullmore, et al., 2001).

[45] See Bullmore on XBAM Method http://www.brainmap.it

2.12.4 TBAM (Talairach Brain Activation Mapping)

In order to extend inference to the group level, the observed and randomised SSQ data for each individual were mapped into standard stereotactic space using a two-stage warping procedure implemented in the TBAM (Talairach Brain Activation Mapping) module of XBAM as described in Brammer et al. (1997) where the statistical maps were aligned with the high resolution structural image and then normalised by transformation onto a Talairach template (Talairach and Tournoux., 1988)[46].

2.12.5 GBAM (Generic Brain Activation Mapping)

The transformation of the statistical maps into standard Talairach space permitted statistical testing at a group level so that a generic brain activation map (GBAM) could be produced. This was achieved by calculating the median of the SSQ ratio at each voxel over all participants (specified in the subjects.txt file) and checking through permutation if the median is significant against the null distribution of the median values from the randomised time series. (The use of median statistics minimised the effects of outliers). The null distribution of SSQ ratios could be thresholded to produce group maps at any level of voxel, or cluster-level to control the risk of type 1 (false positive) error. In the GBAM analysis, the default voxel-level statistical threshold was set to $p < 0.05$ to give maximum sensitivity and to avoid type II errors while the cluster level was set to $p < 0.01$. This process was repeated with an adjusted cluster level threshold as necessary to obtain less than one expected type 1 error per whole brain. The combination of voxel and cluster level thresholds was not derived from theory but rather determined by direct permutation, giving excellent Type I error control (Bullmore et al., 1999). The output files of GBAM were numbered so that 'a1' denoted a noise map, 'a2' was the 1-Back condition compared to the 0-Back baseline task, 'a3' was the 2-Back condition vs 0-Back and 'a4' was 3-Back condition vs. 0-Back.

2.12.6 ABAM (Analysis of Variance Brain Activation Mapping)

The transformation of the statistics maps for each individual into standard space enabled non-parametric analysis of variance tests to be conducted using the second level module called ABAM. The data for each subject and condition was listed in a plain text file (subjects.txt) while the ANOVA factors were specified in the corresponding order in the

[46] This process involved "a rigid body trans-formation of the fMRI data onto a high-resolution inversion recovery image from the same subject, followed by an affine transformation onto a Talairach and Tournoux (1988) template" see http://www.brainmap.it

model DesignMatrix file. A further file (covar.dat) listed the age of the participants on the day of the scan so this could be regressed as a covariate. Group comparison maps were thresholded to obtain less than one false positive cluster.

The second-level analyses conducted were:

- Linear trend analyses:

A within-subject linear trend analysis was conducted for the control and TRS groups using XBAM. This analysis modelled haemodynamic response increase/decrease with successive increase/decrease in cognitive load (i.e. 1-Back < 2-Back < 3-Back).

- Within Group Activations relative to the baseline task:

In addition to the above within subject linear trend analyses, tables for significant within-subject group activations and deactivations (i.e. increases and decreases in the haemodynamic response) relative to group baselines at each level of cognitive load, are provided in the Appendix 2.

- Factorial analysis comparing the TRS and Control groups:

A mixed between-within subject non-parametric analysis of variance was conducted in XBAM where the control and TRS groups formed the between subject factor, and the working memory/cognitive load conditions (1-Back, 2-Back, 3-Back) comprised the within group factor. In the DesignMatrix, the first column coded for the main effect of the group, the second column coded for the main effect of condition/task, while a third coded for the interaction (i.e. column 1 x column 2).

For the reporting of the results, significant clusters smaller than 20 voxels were removed from the analyses. However, the initial analysis obtained some very large clusters. This analysis was subsequently repeated using a voxel p-Value of 0.01 in an attempt to reduce cluster size. However, some very large clusters remained. (The results are shown in tables and figures presented in Appendix 3). Therefore, the large clusters from the first factorial analysis were broken up into Brodmann areas using a declustering technique described at 2.12.7 below and, for the purposes of charting group activations at different levels of cognitive load, to extract SSQs around individual peak activations by applying a relatively small mask (see 2.12.8).

- Factorial analysis comparing the Lower and Higher PANSS groups:

A second mixed between-within subject non-parametric analysis of variance was conducted with age as a covariate which explored the interaction of group (lower PANSS vs higher PANSS) and task condition (cognitive load) using a 2 (group) x 3 (task condition) factorial analysis of covariance. This ANCOVA was conducted with TRS participants grouped according to symptom level based on PANSS scores (procedure as described in section 2.6.1 above).[47] The same statistical approach was taken as above, so the analysis was repeated using a voxel p-Value of 0.01 in an attempt to reduce cluster size. Again, this reduced the number of clusters (the results are shown in Appendix 3), and it was decided to decluster the original analysis.

2.12.7 Declustering Significant Clusters into Brodmann Areas

In order to achieve better localisation and identify more areas within the significant clusters, a "declustering" procedure that is available in the XBAM was applied to the activation maps that were generated after the cluster p-value had been adjusted to minimise the risk of type 1 error (while the voxel p-value was at 0.05). This broke up the significant clusters using cytoarchitectonic areas based on Brodmann Area and resulted in further, generally smaller, clusters of significant activation and a new set of corresponding p-values. As intended, this improved localisation and confirmed the presence of significant activations in brain areas not labelled by XBAM in the earlier analyses. These values are reported in Table 3. 24 and Table 3. 25.

Declustering also produced new statistical maps, however, an option to merge these maps was unavailable for declustered images. However, this actually makes it easier to inspect the many clusters. The reciprocal pattern of task positive and task negative network activity, medially and laterally, is also apparent when presented side by side.

Peaks of activation described by XBAM as being in white matter should be treated with some suspicion as they might arise from an artefact, however distances from the peak activation to the "nearest grey" of less the 5mm were not reported in the tables as they were within the range of normalisation error. Peaks exceeding this were retained and reported if, for example, they related to a large cluster of significant differential activation and there was

[47] A Mann-Whitney U test indicated the difference between ages in the lower PANSS (Median = 35, n =14) and the higher PANSS group (Median = 33, n = 12) was non-significant, U = 65, z = -.979, p = .328, r = 0.19. Under Cohen (1988) guidelines an 'r' value of .1 = small effect and .3 =medium effect so this was considered to be a small to medium effect size. However, as these were small groups and the test might lack sensitivity, age was specified as a covariate.

no clear reason to exclude them. Also, where more than one significant cluster had the same Brodmann area or had common label (e.g. the left medial frontal gyrus with peaks in BA 8 and BA 10), these were reported because to provide a more complete description of the data; also, it cannot be assumed they are functionally equivalent.

2.12.8 Extraction of SSQs following the Declustering Procedure

The declustering option selected in the ABAM module produced new co-ordinates and p-values, however, the extraction of SSQ values for the purposes of charting the haemodynamic response at different levels of cognitive load, was problematic as the application of a mask based on entire Brodmann areas, as opposed to a cluster containing only statistically significant activations, might include "noise" from inactive voxels, those with contrary activations or perhaps increase the risk from physiological artefacts. It was therefore decided to minimise these issues by sampling the immediate area around the peak voxel of significant activations (or deactivations) through the use of a mask. This was achieved by growing spheres with a 2mm radius (34 cubic mm), around each peak co-ordinate and applying this for the extraction of SSQ values. As computations in XBAM use median values, the median value of the SSQs for each condition in each group were plotted in graphs, which are presented in sections 3.10 and 3.11.

The size of sphere was chosen after consideration of the typical thickness of the human cerebral cortex which according to Fischl (2000) has an overall average of 2.5mm (1 - 4.5 mm), with crowns being typically 0.5mm thicker than the sulci. The choice of sphere was also influenced by Tong et al. (2016) who explored various ways of measuring ROIs in the N-back task and optimised observations by restricting selection to a small area around peak voxels. In this instance, it may have been desirable to use a slightly larger mask, however, the program only permitted integers for this function and a sphere with a 3mm radius would have equated to 113 cubic mm which was considered too large for this purpose given the smaller size of some clusters.

In the depiction of contrasts between the TRS and control groups, activation at the corresponding co-ordinates in the contralateral hemisphere is shown for the putamen and thalamus to indicate the direction and degree of activation. Similarly, in the depiction of a contrast for involving the TRS participants grouped according to their general level of symptoms (lower and higher PANSS) involving the left claustrum, the corresponding area for the healthy control group is also shown for comparison to indicate the direction and

degree of activation in this group even though the contrast was not significantly different in the factorial analysis.

2.13 **Correlations between the Haemodynamic Response and other Variables.**

BBAM is an analysis available within XBAM which enables relationships between the haemodynamic response in different brain areas with other variables to be explored through correlational analysis. As with other XBAM analyses, the results do not require adjustment for multiple comparisons. In all the BBAM analyses, the non-parametric Kendall rank correlation coefficient was selected and performed with two covariables: age and mean reaction times in the baseline condition (Is it X?). Mean reaction times in the least demanding 0-Back task for each participant were chosen as a further covariable for this narrow subset of analysis to limit the influence of factors related to the preparation and execution of motor responses which, potentially, might have been affected by earlier treatment with neuroleptic medication although participants had been screened by requiring them to produce sequences of finger movements. Controlling individual mean reaction times also served to better isolate factors relating to the BBAM correlate of mean standard deviations in the 0-Back condition.

Exploratory correlational analyses were conducted for the TRS data for each level of cognitive load between the haemodynamic response and:

- the total number of positive symptoms;
- the total number of negative symptoms;
- mean standard deviations in the 0-Back condition (proposed as proxy for sustained attention) in the TRS group;
- estimated full-scale IQ, with further correlations involving the subscales.

A corresponding analysis was conducted for the control group for mean standard deviations in the 0-Back condition.

The results of the correlations with positive and negative symptoms are reported in section 3.12, with statistical maps and plots of significant correlations. The remaining correlations are provided in Appendix 6. Three figures concerning the control group involving correlations between the haemodynamic response and mean 0-Back SDs were replotted after an extreme outlier was removed, however it was not necessary to repeat the analyses.

CHAPTER III - RESULTS

Results Part I: Demographic, Clinical, Behavioural and Neuropsychological Characterisation of the TRS Group

3.1 Demographic and Clinical Data

Out of 250 individuals who expressed an initial interest by taking a participant information sheet, only 26 participated in the fMRI study. Some potential participants met exclusion criteria, or there were MRI safety concerns. Two did not have a diagnosis of schizophrenia but were receiving clozapine for the treatment of bipolar disorder. Others had expressed an interest "out of politeness" or excluded themselves citing claustrophobia. Some clozapine clinics were s considerable distance away from the IOPPN, so the complexity of the journey as well as the demanding nature of the study may have been considerations.

Demographic information for the TRS and healthy control groups is shown in Table 3. 1, where it can be seen there were no significant differences between the TRS and control groups with respect to gender or ethnicity, however, the TRS group was significantly older, by an average of 7 years.

As previously stated, the control group did not participate in neuropsychological and clinical assessments, nor was information about years of education, smoking or historic drug use collected. However, even without a comparison group, there appeared to be a very high prevalence of smoking among TRS participants at 76%, moreover 92% (23/25) indicated they had been nicotine-dependent at some point, (continued in Table 3 .2).

Table 3. 1 Demographic Information for the TRS and Control Groups

	TRS Participants	Healthy Controls	Statistic
Mean Age (SD, range, n)	36 years (7.67, 25-54, 26)	29 years (6.71, 20-46, 21)	t (45) = -3.285, p = .002***
Female	8 (30.7%)	7 (33.3%)	
Male	18 (69.3%)	14 (66.7%)	χ^2 (1, n=47) = .000, p = 1.000, phi = .027¬¬¬
Ethnicity: Caucasian	15 (57.7%)	18 (85.7%) ¬	χ^2 (1, n=33) = .27 p = .602¬¬¬
Black British	5 (19.2%)	1 (4.76%)	
Afro-Caribbean/Caucasian	3 (11.5%)		
African ¬	2 (7.7%)		
Anglo/Indian	1 (3.9%)		
Asian		1 (4.76%)	
SE Asian		1 (4.76%)	
Diagnosis¬¬ Schizophrenia	23/26 (88.5)	-	
Schizo-affective disorder	3/26 (11.5%)	-	
Smokes tobacco	19/25 (76%) ¬¬¬¬	-	

¬ English was not the first language but was the preferred language of two TRS participants having spoken it since childhood, while one control participant was highly fluent in English although their first language was Russian.

¬¬ One participant had been diagnosed with schizo-affective disorder 8 year's previously but was currently diagnosed with paranoid schizophrenia. Another was taking the mood stabiliser Lithium Carbonate along with clozapine but was diagnosed with paranoid schizophrenia.

¬¬¬ χ^2 with Yates Continuity Correction;

¬¬¬¬ 92% had been regular smokers at some point

*** Significant after Bonferroni correction with an adjusted alpha of p = .017; the eta squared statistic (.19) for the difference in mean age indicated a large effect size according to guidelines proposed by Cohen 1988, pp. 284-7.

3.1.1 Characteristics of TRS groups based on Symptom Severity

As can be seen from Table 3. 2, the age difference between the lower and higher PANSS groups was not significant, nor did the distribution of the sexes differ. However, the prevalence of smoking was significantly greater in the higher PANSS group at 90.9%, compared to 64.3%. Information on substance use prior to the first episode of psychosis is supplied in Table 3. 4.

Table 3. 2 Demographic Information for the TRS Participants Grouped According to Symptom Severity

	Lower PANSS Group	Higher PANSS Group	Statistic
Median Age (Interquartile range, n)	35 years (10, n=14)	33 years (14, n=12)	z = -1.031, r = -0.2022, U =64, p = 0.303
Female	4 (28.6%)	4 (33.3%)	p = 1.000, Fisher's Exact
Male	10 (67.4%)	8 (66.7%)	
Smokes tobacco	9 (64.3%)	10 (90.9%)	χ^2 (1, n=25) = 6.76 p = .009**

Note: Individuals in the lower PANSS group exhibited a generally very low level of psychopathology with total scores on the PANSS scale below 41. Two of the three participants with a diagnosis of schizo-affective disorder were in the lower PANSS group.

3.1.2 Comparison of Clinical Variables in the Lower and Higher PANSS Groups

Table 3. 3 supplies information concerning aspects of clinical history, treatment and symptoms. In view of concerns that acute psychosis could be neurotoxic, further exploratory correlations were conducted concerning the time to access clozapine from the initial diagnosis, also with the duration of treatment with clozapine (methods 2.7.3). Most were non-significant and are shown in Table Appx. 4. 7.

Table 3. 3 Summary of Clinical Variables, Comparing Lower and Higher PANSS Groups

	TRS (n=26)	Lower PANSS (n=14)		Higher PANSS (n=12)		Statistic: Mann-Whitney U Test			
	Median, (Interquartile range)	Min-Max	Median	Min-Max	Median	z	r	U	p
Age at First Episode of Psychosis	20 (6.75)	17-32	21	15-28	20.0	-0.914	0.179	60.5	0.361
Years before a trial of clozapine after diagnosis	6.6 (5.93)	0.5-11	4	0.5-17	7.0	-1.864	0.366 [b]	43	0.062
Age stabilised on clozapine	26.5 (13.25)	18 -39	25.5	19-45	27.5	-0.644	0.126	71.5	0.519
Years on clozapine	7.5 (6.75)	0.6-16	9.5	0.1-15	4.5	-2.398	0.470 [b]	37.5	0.016*
Years unwell since FEP	14 (8.75)	9 -24	14	7-26	10.0	-0.604	0.119	66	0.546
PANSS Total	45 (26)	37-45	41	51-90	66.0	-4.332	0.850 [c]	0	0.001*
Total Positive Symptoms	11 (7)	7 -12	8.5	10-26	15.0	-4.021	0.789 [c]	4	0.001*
Total Negative Symptoms	14 (9)	8 -17	11	11-28	20.0	-3.518	0.690 [c]	13	0.001*
Total General Symptoms	24 (9)	17-26	21	27-45	29.0	-4.231	0.830 [c]	0	0.001*
* $p < 0.05$ (Bonferroni correction for 17 comparisons between higher and lower PANSS p= .003 in Tables 3.2, 3.3 and 3.4). Guidelines proposed by Cohen (1988), pp. 284-7: [a] 0.1 indicates small effect size [b] 0.3 medium effect size [c] 0.5 large effect size									

3.1.3 Substance Use

Table 3. 4 provides an overview of estimated exposure to illicit drugs or excessive alcohol consumption by individuals in the TRS group before their FEP between 1985 and 2003. The availability and variety of drugs has changed considerably since so a more comprehensive description and analysis concerning this unique cohort is supplied in Appendix 1.

Only 12% of the TRS group indicated they had abstained, while a third had experienced at least four different kinds of drug. The most commonly tried were cannabis (used by 64%) and LSD (used by 40%). There were no significant differences regarding the type of drug used between the lower and higher PANSS groups.

Table 3. 4 Drugs of Abuse commonly tried before the First Episode of Illness

Prior to First Episode	PANSS Groups Combined (%)	Lower PANSS (%)	Higher PANSS (%)	Statistic comparing Higher and Lower PANSS
No drug use	12	12	0	χ^2 (1, n=25) = 1.034, p = .309, phi =.327 ¬¬¬
Four or more types	32	20	12	χ^2 (1, n=25) = 0.001, p = .986, phi = .090 ¬¬¬
Cannabis	64	36	28	χ^2 (1, n=25) = 0.001, p = 1.000, phi = .007 ¬¬¬
LSD	40	16	24	χ^2 (1, n=25) = .818, p = .366, phi = -.263 ¬¬¬

Notes: Based on recall of approximate age when a drug was first tried. This was subsequently related to age at first admission for psychosis from records.
4% = 1 individual.
¬¬¬ χ^2 with Yates Continuity Correction.
Bonferroni correction for 17 comparisons between lower and higher PANSS in Tables 3.2, 3.3, 3.4 p= .003.

Figure Appx. 1. 1 depicts the above along with other drugs, while in Figure Appx. 1.2 it is estimated that 72% of the TRS group had pharmacological exposure to drugs which boost dopamine and 48% were exposed to serotonergic agents at some point prior to their first episode of psychosis (FEP).

3.2 IQ estimated with the WASI

One of the TRS participants was considered too unwell to take part in neuropsychological testing so the WASI was administered to 25 participants (8 females (31%), 17 males (69%). The standard scores were normally distributed, and the group means for full-scale IQ, verbal IQ and performance IQ scores clustered around the population norm (100). As shown in Table 3. 5, mean estimated full-scale was IQ higher in the lower compared with the higher PANSS group, p =.04, with a large effect size, although, group differences on the subscales were not significant.

In addition, there was a correlation between years spent in education and full-scale IQ scores: p = .573, n=25, p = .003. Scores on the verbal and performance subscales were positively correlated, r = 532, n =25, p = .006. (Again, this was no longer the case when split into lower and higher PANSS groups, r = .421, n=14, p = .134 and r = .497, n=11, p = .119, respectively).

Table 3. 5 Comparison between Lower and Higher PANSS Groups for WASI Standard Scores and Years of Education

	TRS (n=25)	Lower PANSS (n=14)	Higher PANSS (n=11)		Statistic		
	Mean (SD)	Mean (SD)	Mean (SD)	df	t	p	Eta ^{2}
Years of Education	13.28 (2.05)	14 (1.51)	12 (2.28)	24	2.008	.056	.14
Full-scale IQ	101.68 (14.63)	106.93 (11.24)	95 (16.17)	23	2.176	.040*	.17
Verbal IQ	100.24 (17.41)	105.36 (14.30)	93.73 (19.50)	23	1.724	.098	.11
Perform-ance IQ	102.28 (12.75)	106.29 (8.9)	97.18 (15.36)	23	1.861	.076	.13

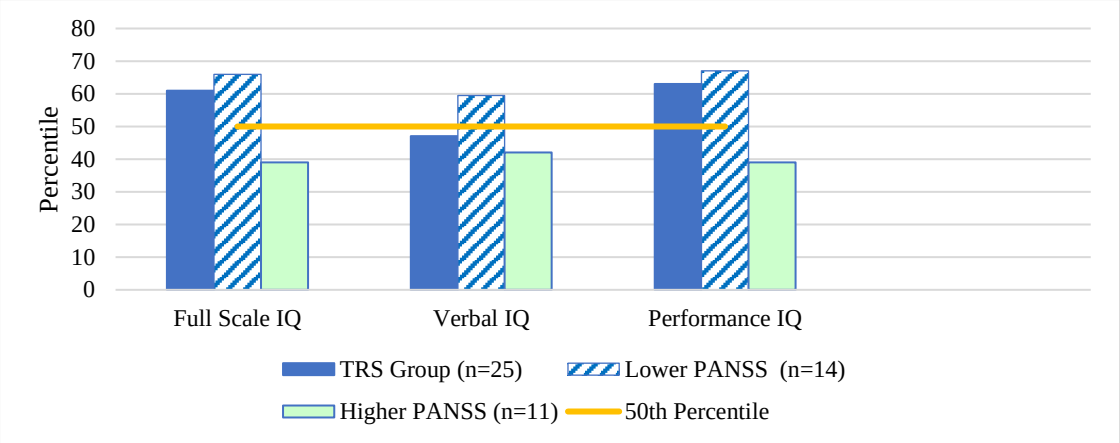
* $p < 0.05$ (adjusted alpha for 4 comparisons would be p = 0.0125).
The eta squared statistic indicates large effect sizes in this table as Cohen (1988, pp.284-7) proposed .01, .06 and .14 indicate small, medium and large effect sizes respectively.

3.2.1 Comparison of Estimated IQ Scores with Population Norms

Estimated IQ scores were also expressed in percentiles so they could be readily compared against a marker line in Figure 3. 1 representing the 50th percentile, for the general population. Some heterogeneity became apparent as the median FIQ and PIQ scores across the TRS group as a whole were higher than the 50th percentile by 11 and 13 percentiles

respectively, while the median VIQ score was 3 percentiles below this. Also, while scores in the higher PANSS group were relatively depressed, they were still within 8-11 percentiles of the peak of the normal distribution, so comfortably within the normal range.

Figure 3. 1 Median IQ Scores for the TRS Group (expressed in percentiles)



IQ Scores in Percentiles:	Full-scale IQ (interquartile range)	Verbal IQ (interquartile range)	Performance IQ (interquartile range)
TRS Group (n=25)	61 (49)	47 (51)	63 (39)
Lower PANSS (n=14)	66 (42)	59.5 (39)	67 (24)
Higher PANSS (n=11)	39 (52)	42 (56)	39 (51)

3.3 Asymmetries between the WASI Subscales

Visual inspection of individual scores (graphically illustrated in Figure 3. 2) revealed an unexpected observation of marked asymmetries between the subscales for some participants, with most favouring performance IQ. However, this finding could be a consequence of using the WASI as a measure of IQ (Ryan and Brown, 2005; also see discussion at 4.2.7). Using the threshold of a 10-point difference, described in methods (section 2.7.1), 52% (13/25) of participants exhibited an asymmetry: in 16% of cases (4/25), VIQ was superior to PIQ, while in 36% (9/25), PIQ was superior to VIQ. The three groups to emerge from this procedure are described below in Table 3. 6. Only four individuals comprised the superior VIQ group with standard VIQ of 104, 127, 129 and 130 which were in marked contrast with the corresponding PIQ scores: 88, 84, 110 and 105.

Table 3. 6 Description of IQ asymmetry groups based on individual differences between verbal and performance subscales in TRS participants*

Median of Standard IQ Scores	Full-scale IQ	Verbal IQ	Performance IQ	Subscale Asymmetry
Superior VIQ (16%, n=4) (interquartile range)	111.5 (24)	128 (20)	96.5 (24)	22 (22)
Superior PIQ (36%, n=9) (interquartile range)	99 (24)	91 (26)	105 (16)	-15 (10)
No Asymmetry (48% n=12) (interquartile range)	103 (16)	101 (13)	104 (17)	-1.5 (5)

* Asymmetry if difference in standard scores is 10 points or more.

Figure 3. 2 Individual Asymmetries in Performance between WASI Subscales

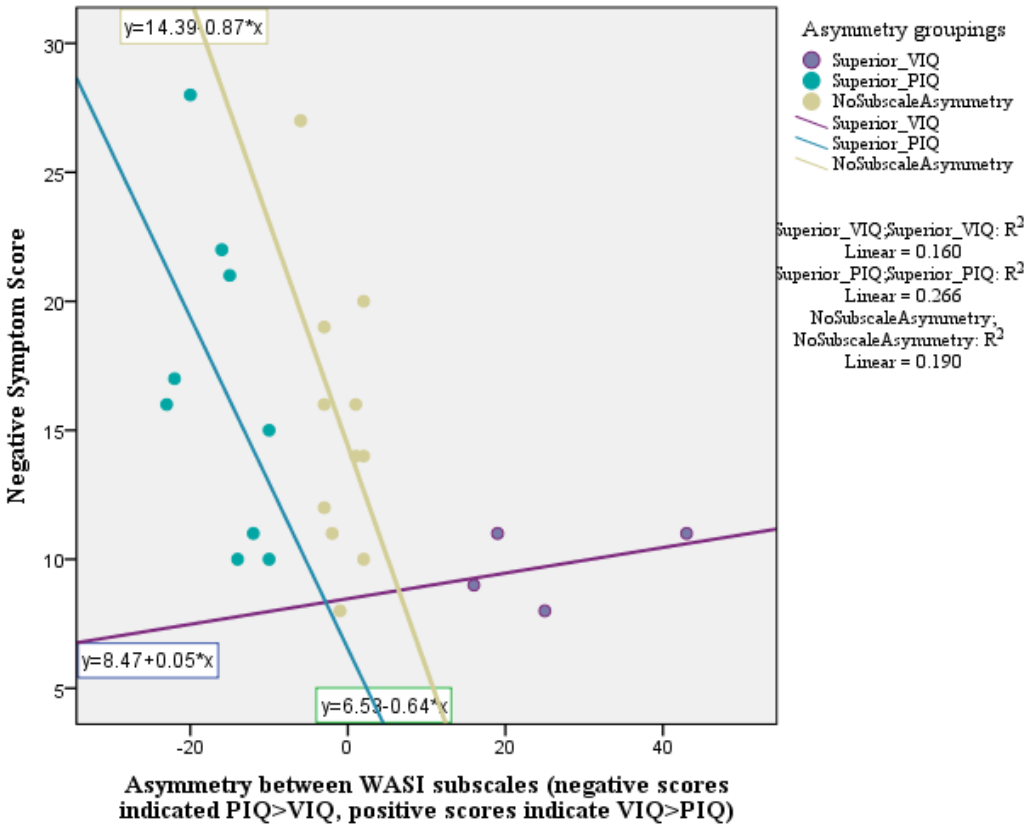
	Subscales:		Difference	Asymmetry	Difference
Case No	Verbal	Performance	Standard Scores	Percentiles	Percentiles
15	81	104	-23	10 < 61	-51
23	78	100	-22	7 < 50	-43
44	76	96	-20	5 < 39	-34
48	111	127	-16	77 < 96	-19
27	55	70	-15	0.1 < 2	-1.9
40	91	105	-14	27 < 63	-36
25	106	118	-12	66 < 88	-22
13	99	109	-10	47 < 73	-26
24	99	109	-10	47 < 73	-26
19	106	112	-6	66 < 79	-13
12	103	106	-3	58 < 66	-8
18	99	102	-3	47 < 55	-8
26	86	89	-3	18 < 23	-5
10	113	115	-2	81 < 84	-3
22	106	108	-2	66 < 70	-4
43	120	121	-1	91 < 92	-1
41	88	87	1	21 < 19	2
46	97	96	1	42 < 39	3
8	98	96	2	45 > 39	6
11	95	93	2	37 > 32	5
14	109	107	2	73 > 68	5
17	104	88	16	61 < 21	40
9	129	110	19	97 > 75	22
38	130	105	25	98 < 63	35
45	127	84	43	96 < 14	82

(TRS: N = 25)

The asymmetry between the WASI subscales was also considered in relation to overall symptom levels: 57.1% (8/14) of individuals in the lower PANSS and 41.7% (5/12) in the higher PANSS groups exhibited an asymmetry between the IQ subscales. A Chi-square test for independence (with Yates Continuity Correction) confirmed there was no significant association between lower/higher PANSS membership and asymmetry in the subscales, χ^2 (1, n= 25) =.03, p = .859, phi = .116.

However as can be seen from Figure 3. 3 below, depicting the correlation between negative symptoms and the degree of asymmetry between the subscales (reported in Table 3. 18), the four participants with superior VIQ scores also had a low level of negative symptoms (scores ranging from 8-11), to the extent this approximated to a "floor effect". (Also see inset for the same correlation at 3. 3 (b). This indicates the higher the level of negative symptoms the more likely an individual will exhibit a decrement on the verbal subscale).

Figure 3. 3 Correlation between Negative Symptoms and Asymmetry between the WASI subscales.



n=4 (16%) superior scores on the verbal IQ subscale; n=9 (36%) superior scores on the performance IQ subscales; n=12 (48%) no asymmetry between the subscales

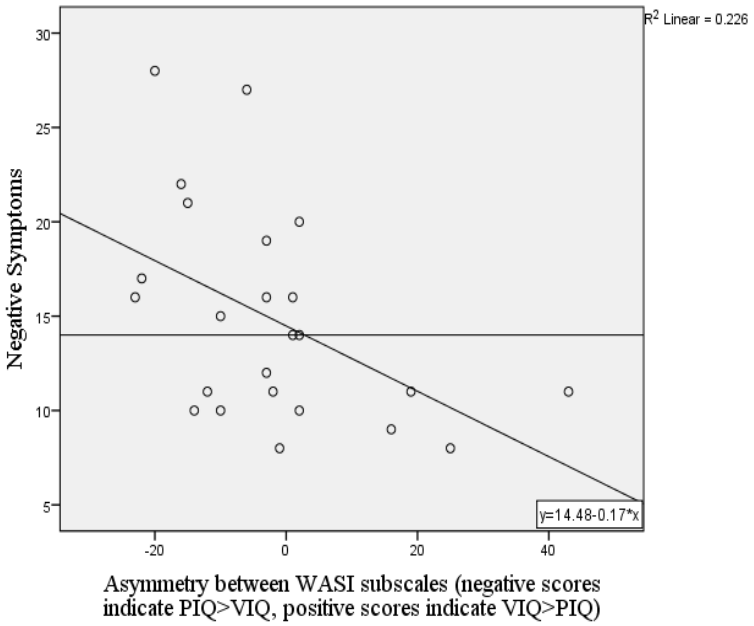


Figure 3. 3 (b) (inset)

Depicts the same correlation but without the marking of asymmetry groupings, while the horizontal line shows the median of negative symptom scores (n=24).

The "superior VIQ" subgroup is too small for inferences based on neuropsychological profiles and clinical history; however, it is noted FIQ standard scores ranged from 96 - 123 and one participant was (unusually for the group) in regular employment and two had returned to higher education. They differed in further respects (described in Table 3. 19; also, see Figures Appx. 5.1, 5.2, 5.3).

3.4 The MCCB Test Battery Results

One of the TRS participants was considered too unwell to take part and another was unavailable for the MCCB test battery so the following results, summarised in Figure 3. 4 with the related data in Table 3. 7, are based on 24 participants. The TRS group and subgroups (i.e. higher and lower PANSS) scores were consistently below the 50th percentile of the normative sample, indeed most were below the 16th percentile. This applied even to the lower PANSS group that had a median FIQ at the 66th percentile. The best performance on an individual test was for the category fluency word generation task (animal names), while the worst was observed for social cognition which approached 2SDs below the mean. On both tests, there was no difference in the median scores for the lower and higher PANSS subgroups. Indeed, there were no significant differences between these symptom groups for any of the tests (Table 3. 7). The only difference between lower and higher PANSS groups on a single test that approached significance concerned visual learning, p = .077, (the marked discrepancy in relative to scores for the TRS group as a whole apparent in

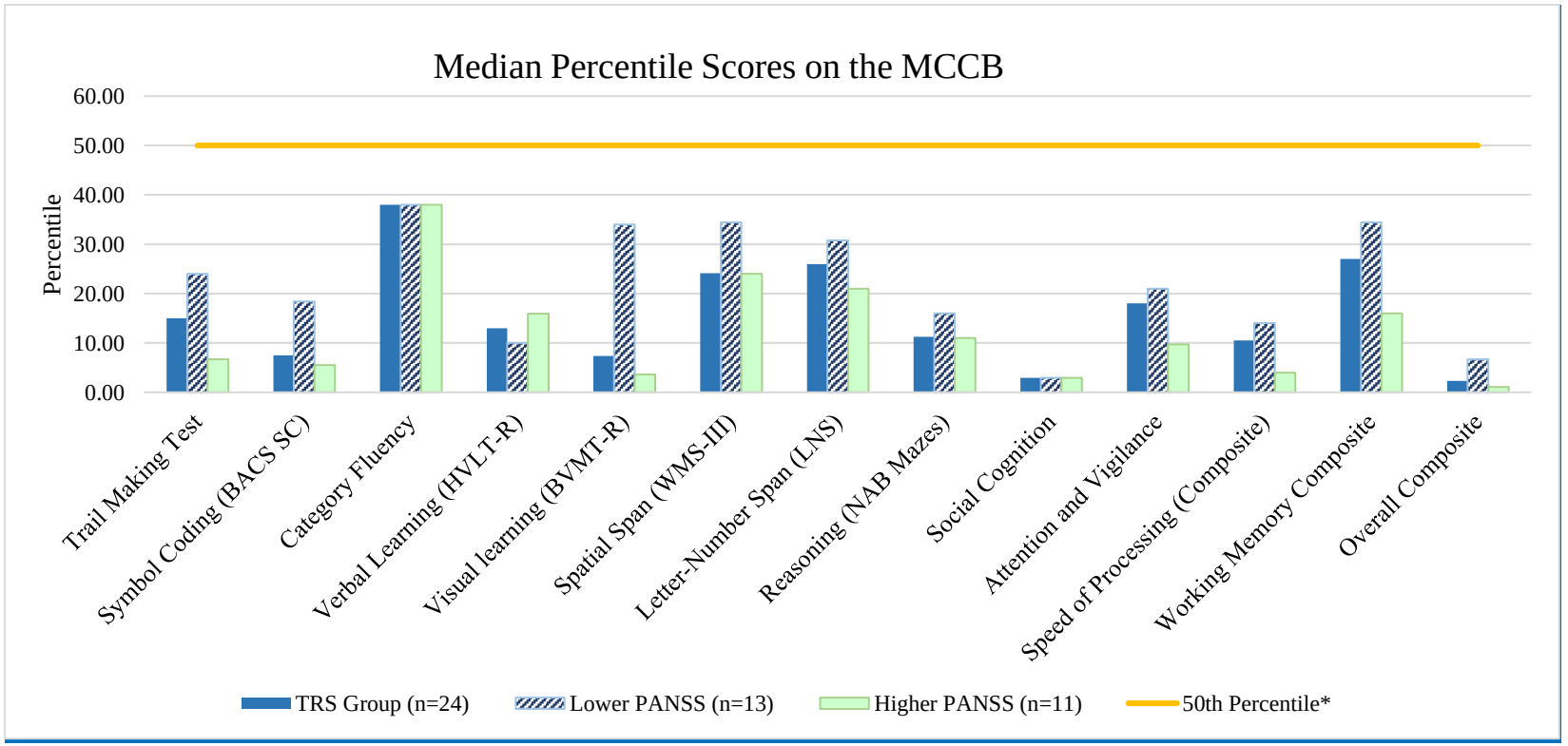
Figure 3. 4 being due to median statistics). While the speed of processing composite had trend significance ($p = .056$) with a medium effect size.

As this study does not include a group of participants who responded to first line antipsychotics, the T-scores on the MCCB domains are compared with those provided in some published studies concerning "participants with schizophrenia" (PSZ). These are shown in appendix 4 (Table Appx. 4. 8, Figure Appx 4. 1) and indicate a fair degree of similarity across studies and participant groups, with further validation of the MCCB norms at the 50th percentile by the large healthy control group in Johnson et al. (2013).

In order to further evaluate the heterogeneity in this study, a series of within-participant comparisons were conducted comparing their category fluency scores with performance in other domains (described in methods 2.7.2). The results are shown in Table 3. 7 and reveal highly significant differences with medium effect sizes for most tests, although, the differences between category fluency and working memory (spatial span and verbal span) were not significant. Appendix 4, Table 4. 2, provides further context by summarising a series of exploratory correlations with MCCB composite scores: estimated FIQ and the subscales were highly correlated with the MCCB overall composite; neither category fluency nor the time taken to complete the Trail Making Test correlated with the Speed of Processing Composite to which they contributed, whereas RTs in the 0-Back Condition of the n-back task did. Nonetheless there was a very highly significant correlation between the 'speed of processing composite' with the MCCB overall composite (Table Appx. 4. 2).

Table 3. 9 displays the results of some correlations between MCCB tests of learning and working memory with the WASI scores and MATRICS composite scores to explore their association with higher cognition.

Figure 3. 4 A Comparison of Scores on the MCCB for TRS Groupings with MCCB Population Norm at the 50th percentile



Notes: Adjusted for age and sex.
The horizontal line represents the 50th percentile reflecting population norms derived during the standardisation procedure (Kern et al., 2008).

Table 3. 7 Scores on the MCCB: TRS Grouped According to Symptom Level on the PANSS scale (expressed in Percentiles)

	TRS Group n =24		Lower PANSS n = 13		Higher PANSS n = 11		Statistic: Mann-Whitney U Test			
	Median (interquartile range)		Min-Max	Median	Min-Max	Median	U	z	p	r
Trail Making Test (TMT-A)	15.0	(29.9)	0.1 – 57.9	24	0.1 – 34	6.7	47.5	-1.394	0.163	0.285 [b]
Symbol Coding (BACS SC)	7.5	(38.6)	0.3 – 66.0	18.4	0.6 – 61.8	5.5	47.5	-1.392	0.164	0.284 [b]
Category Fluency	38.0	(46.4)	7.0 – 78.8	38.0	0.2 – 97.7	38.0	63.5	-0.465	0.642	0.095
Verbal Learning (HVLT-R)	12.95	(21.8)	4.5 – 76.0	10.0	0.5 – 81.6	15.9	70.0	-0.087	0.931	0.018
Visual learning (BVMT-R)	7.35	(48.8)	0.2 – 96.4	34.0	0.0 – 38.0	3.6	41.0	-1.769	0.077	0.361 [b]
Spatial Span (WMS-III)	24.1	(36.1)	2.9 – 86.0	34.4	1.1 – 94.6	24.0	57.5	-0.812	0.417	0.166 [a]
Letter-Number Span (LNS)	26.0	(30.6)	8.0 – 69.0	30.8	0.2 – 57.9	21.0	49.5	-1.276	0.202	0.261
Reasoning and Problem Solving (NAB Mazes)	11.25	(18.3)	0.3 – 92.0	16.0	1.4 – 27.0	11.0	53.5	-1.044	0.297	0.213 [a]
Social Cognition (MSCEIT ME)	2.9	(11.2)	0.0 – 99.9	2.9	0.2 – 38.2	2.9	68.5	-0.174	0.862	0.036
Attention and Vigilance (CPT-IP)	18.0	(31.1)	3.6 - 73.0	21.0	0.1 – 38.2	9.7	40.5	-1.798	0.072	0.367 [b]
Speed of Processing Composite (TMT, BACS, Fluency)	10.5	(22.3)	1.4 – 46.0	14.0	0.0 – 79.0	4.0	38.5	-1.914	0.056	0.391 [b]
Working Memory Composite (WMS-III, LNS)	27.0	(30.6)	0.1 – 72.6	34.4	0.6 – 90.3	16.0	43.0	-1.656	0.098	0.338 [b]
Overall Composite * ¬	2.3	(16.4)	0.3 – 57.9	6.7	0.0 – 30.8	1.1	32.5	-2.262	0.024	0.462 [b]

* $p < 0.05$ ¬ Based on a complete dataset (n=24), apart from the CPT-IP (n=18) where missing scores had to be imputed for calculation of the composite. (Adjusted alpha after correction for this family of 13 comparisons: $p = 0.004$)

Guidelines proposed by Cohen (1988), pp. 284-7: [a] 0.1 indicates small effect size [b] 0.3 medium effect size [c] 0.5 large effect size

3.4.1 Heterogeneity in MCCB Task Performance Compared with Category Fluency

Table 3. 8 Comparisons between Category Fluency Scores and other MCCB measures

	Median Percentile (Interquartile range)	Z	r	p
Letter-Number Span (LNS)	26.0 (11.5 - 42.1)	-1.840	.266 [b]	.066
Spatial Span (WMS-III)	24.1 (15.9 - 52.0)	-1.329	.192 [a]	.184
Attention and Vigilance CPT-IP)	18.0 (4.3 - 35.4)	-2.658	.384 [b]	.008**
Trail Making Test (TMT-A)	15.0 (3.3 - 33.2)	-2.920	.422 [b]	.004***
Verbal Learning (HVLT-R)	13.0 (5.5-27.3)	-3.129	.452 [b]	.002***
Reasoning and Problem Solving (NAB Mazes)	11.3 (8.0 - 26.3)	-2.613	.377 [b]	.009**
Symbol Coding (BACS SC)	7.5 (2.5 - 41.1)	-2.783	.417 [b]	.005***
Visual learning (BVMT-R)	7.4 (1.2 - 50.0)	-2.386	.344 [b]	.017*
Social Cognition (MSCEIT ME)	2.9 (0.43 - 11.6)	-3.452	.498 [c]	.001***

Note: The median and interquartile range of scores on the category fluency test (expressed in percentiles) were 38 (19.5-65.9), n=24.
* = significant at $p < .05$. ** = significant at $p < .01$.
*** = significant after Bonferroni correction for this family of 9 comparisons with an adjusted alpha = .006
Guidelines proposed by Cohen (1988), pp. 284-7: [a] 0.1 indicates small effect size [b] 0.3 medium effect size [c] 0.5 large effect size

3.4.2 Some Correlations between the MCCB Overall Composite, Learning and WASI Subscales

Table 3. 9 Inter-correlations between learning/short-term memory, the WASI subscales and the MCCB Overall Composite Score

		MCCB Overall Composite	Estimated Performance IQ	Estimated Verbal IQ	Visual Learning (BVMT)	Visual WM Spatial Span	Verbal Learning (HVLT-R)	Verbal WM (LNS)
MCCB Overall Composite Score (percentiles)	Pearson Correlation	1.000						
	Sig. (2-tailed)							
	N	24						
Estimated Performance IQ	Pearson Correlation	¬ .689**	1					
	Sig. (2-tailed)	.001						
	N	24	25					
Estimated Verbal IQ	Pearson Correlation	¬ .536**	.532**	1				
	Sig. (2-tailed)	.007	.006					
	N	24	25	25				
Visual Learning	Pearson Correlation	¬ .818**	.598**	.449*	1			
	Sig. (2-tailed)	.001	.002	.028				
	N	24	24	24	24			
Visual Working Memory (Spatial Span)	Pearson Correlation	¬ .492*	.475*	.098	.311	1		
	Sig. (2-tailed)	.015	.019	.648	.139			
	N	24	24	24	24	24		
Verbal Learning/ STM (HVLT-R)	Pearson Correlation	¬ .415*	.392	.578**	.476*	.148	1	
	Sig. (2-tailed)	.043	.058	.003	.019	.490		
	N	24	24	24	24	24	24	
Verbal Span/ Working Memory (Letter Number Sequence)	Pearson Correlation	¬ .647**	.688**	.593**	.541**	.370	.431*	1
	Sig. (2-tailed)	.001	.001	.002	.006	.075	.035	
	N	24	24	24	24	24	24	24

¬ Spearman's Rho was used in this correlation. * Correlation significant at the 0.05 level; ** Correlation significant at the 0.01 level.
Bonferroni correction for a family of 21 comparisons: p = .002. According to Cohen (1998, pp. 79-81) a correlation coefficient is strong if it is between .5 and 1.0.

3.4.3 MCCB Variables and the Time to access Clozapine

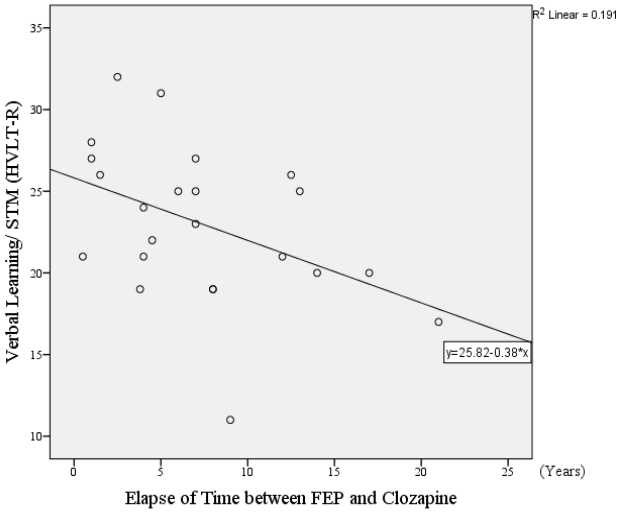
There was a negative correlation between the time to access clozapine and the overall MCCB composite (rho = -.549, n=23, p = .007), indicating worse scores were associated with longer delays. In addition, there were significant negative correlations between the time to access clozapine and short-term learning/memory (visual and verbal), which remained significant after partial correlation controlling for age. These are reported below and shown in Figures 3.5 and 3.6.

Moreover, there was a negative partial correlation between the elapse of time between the first episode of psychosis and visual learning, controlling for age at the time of the study: r = -.621, n=23, p = .002. Inspection of the zero-order correlation (r = -.521) indicates age had a modest effect of the strength of the relationship.

In addition, there was a significant negative partial correlation between the elapse of time between the first episode of psychosis and verbal learning, controlling for age at the time of the study, r = -.531, n=23, p = .01. Inspection of the zero-order correlation (r = -.438) indicates age had a modest effect of the strength of the relationship. Further, when just the scores on the first trial of the HVLT-R were considered with age as a covariate, the result was very similar: r = -.523, n=23, p = .012.

Figure 3. 5 Negative Correlation between Verbal learning and Time to access Clozapine

(a) TRS Group (n=23)



(b) With lines of best fit for Lower and Higher PANSSGroups

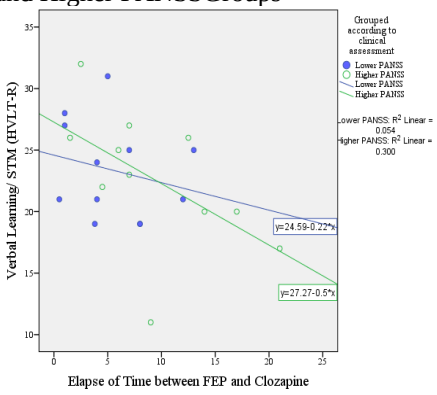
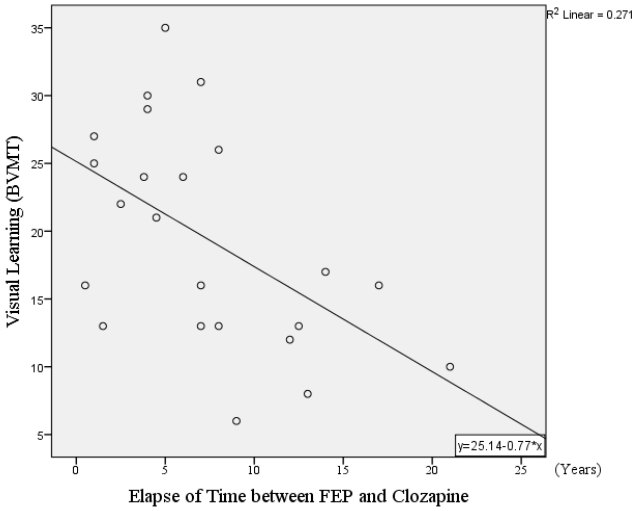
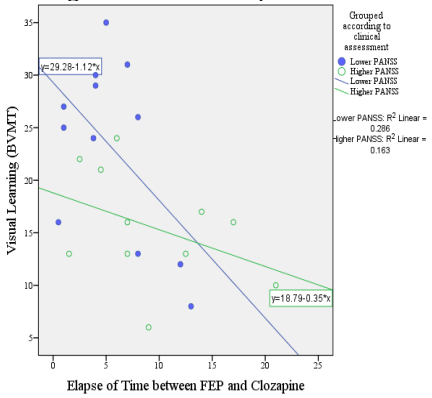


Figure 3. 6 Negative Correlation between Visual learning and Time to access Clozapine

(a) TRS Group (n=23)



(b) With lines of best fit for Lower and Higher PANSSGroups



According to Cohen (1988, pp, 79-81), all the correlations in this section might be described as strong after controlling for age, since the r-values were between .5 and 1.0.

3.5 A Post Hoc Analysis of Serial Position in Free Recall (HVLT-R)

Free recall following the first presentation of the list appeared normal (Miller, 1956) ranging from 4 to 8 items recalled out of a possible 12. The median number of items recalled was 6 in both the lower and higher PANSS groups, and a Mann-Whitney U Test confirmed there was no significant difference: lower PANSS (Md=6, n=13), higher PANSS (Md=6, n=11), U = 59.50, z = -.728, p = .494, r = .15. However, as referred to in Methods section 2.7.2, a post hoc analysis of recall on the first trail of the Hopkins Verbal Learning Test was carried out to examine whether there was a recency effect which is thought to reflect the contents of a short term store that is briefly available following auditory presentation (Vallar, 2007). This revealed that, behaviourally, 92% (22/24) of TRS participants did not begin their free recall with the last item from the list of 12 words. Indeed, only 12.5% (3/24) started their recall with any item from amongst the last 3 positions.

Figure 3. 7 depicts recall for items at their list positions, without reference to the order in which items are recalled. As expected, a primacy effect is discernible, yet, despite the supra-span length of the list, recall for the last two items was modest, while recall at position 10 resembles the asymptote. As recall at the recency portion can exceed that of the first portion, this curve suggests an attenuated, or absent recency effect.

A more detailed description of the omissions that occurred at the last three positions for repeated presentations of the same list is available for reference in Table Appx. 4. 1. By the third trial the number of individuals recalling all three items had risen to 42%, while 87.4% recalled 2 items from the last three positions, however, it is not possible to differentiate between the effects of learning and changes in strategy to use the recency effect.

Regarding recall for items at the start of the list, it is possible some participants preferred to recall items in the order in which they were presented despite instructions they could recall the words in any order. A description of the frequencies at which items were recalled in their list order at the first three positions on the first trial is provided in Table 3. 10 below. From this is can be seen only one individual recalled all three items in their list order, so it seems unlikely this was a common strategy since 3 items should be within the capacity of short-term memory.

Figure 3. 7 Serial Position Curve for the First Trial of the Verbal Learning Test (HVLT-R)

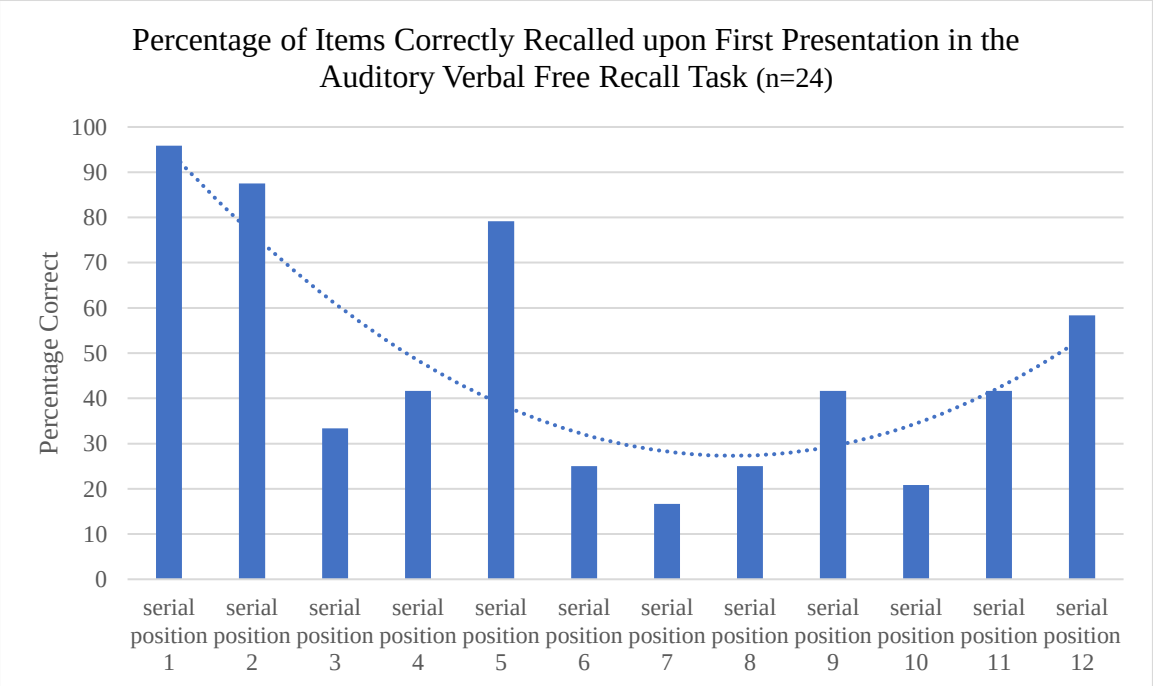


Table 3. 10 Serial Learning as a Strategy?

	1st item: "Lion"	2nd item: "Emerald"	3rd item: "Horse"
Lower PANSS (n=13)	76.9% 10/13	61.5% 8/13	7.7% 1/13
Higher PANSS (n=11)	54.5% 6/11	36.4% 4/11	0% -
All TRS (n=24)	66.7% 16/24	50% 12/24	4.1% 1/24

3.6 On-line Behavioural Data Collected during the Verbal N-Back

The non-parametric nature of the behavioural data, including that for omission errors, was confirmed by the Kolmogorov-Smirnov statistic below.

Table 3. 11 Kolmogorov-Smirnov Test of Normality for the Behavioural Data

Reaction Times	0-Back	1-Back	2-Back	3-Back
TRS (n=26)	.022*	.053	.200	.200
Controls (n=21)	.001*	.022*	.047*	.200
Standard Deviations	0-Back	1-Back	2-Back	3-Back
TRS (n=26)	.001*	.200	.200	.200
Controls (n=21)	.001*	.002*	.024*	.200
Number of Omission Errors	0-Back	1-Back	2-Back	3-Back
TRS (n=26)	.001*	.001*	.001*	.001*
Controls (n=21)	.001*	.001*	.001*	.113

*A significance value of less than .05 indicates the distribution is not normal.

3.6.1 Reaction Time Data (Processing Speed)

Mean reaction times across the entire n-back task, without intermediate computation for the experimental conditions, were 509.05ms (SD = 87.20) in the control group and 609.50ms (SD = 132.36) in the TRS group, i.e. 19.73% slower overall in the TRS group. An independent-samples t-test revealed this difference was significant, t (45) = -2.990, p = .005. The magnitude of the difference (mean difference = 100.45, 95% CI: -168.11 - 32.77) was large (eta squared = .166).[48]

[48] Cohen (1988, pp.284-7) proposed an eta squared of .01, .06 and .14 indicated small, medium and large effect sizes respectively.

As can be seen in Figure 3. 8, reaction times were slower at each level of cognitive load. The differences between the groups (Table 3. 12 below) were significant at every level, apart from the 2-back condition where the difference approached significance at p = 0.054. However, most would not survive Bonferroni correction restricted to this set of comparisons with an alpha level of 0.0125. Following Nakagawa (2004) above, the effect sizes reflected in the 'r values' were also considered. Applying Cohen's (1988) guidelines, the differences between median reaction times were very large in the 0-back condition and large in the 1-back; however, in the 2-back condition there was a medium effect size and in the 3-back condition it was negligible.

In case this pattern might be explained by a high level of errors distorting values, the scores of one TRS participant (who made 4/9 correct responses in the 2-Back condition) and two controls (who made 4/9 and 3/9 correct responses in the 3-Back condition) were removed and the Mann-Whitney tests were repeated. These revealed a similar result in the 2-Back condition where there was no significant difference in reaction times between TRS (Md = 611.44ms, n = 25) and control groups (Md = 546.71ms, n = 19), U = 183, z = -1.753, p = .08, r =.258 (a small effect size)[49]; but there was a significant difference between TRS (Md = 753.0ms, n=25) and control groups (Md = 631.11ms, n = 19), U = 149, z = -2.097, p = .036, r = .316 (a medium effect size) in the 3-Back condition. However, again these differences would not survive the Bonferroni correction with alpha at 0.0125, in contrast to those at lesser levels of cognitive load.

The use of median statistics minimises the influence of more extreme scores and the pattern of convergence in reaction times between the two groups is clearer when the data is described using mean reaction times (screened for outliers 2.5 SD above the mean): RTs were slower in the TRS group relative to the control group, by 30.16% in the 0-Back 24.16% in the 1-Back, 15.7% in the 2-Back and 15.5% in the 3-Back conditions.

[49] Cohen (1988): r =.10, .30 and .50 for small, medium and large effect sizes respectively

Figure 3. 8 Comparison between TRS and control groups of median reaction times at each level of the N-Back Task.

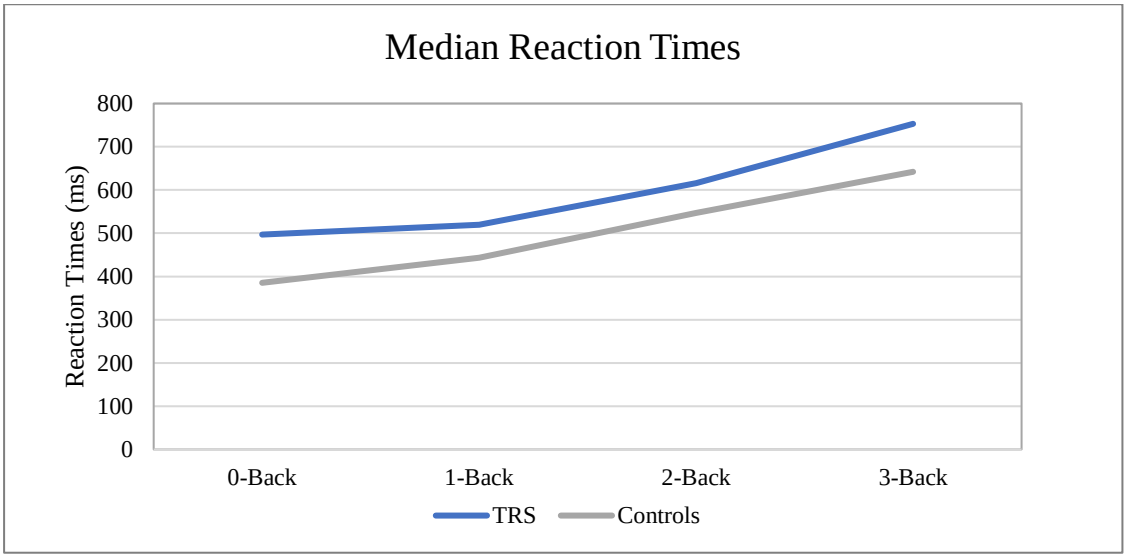


Table 3. 12 Comparison of Median Reaction Times (ms) at each Level of Cognitive Load on the N-Back Task

Cognitive Load	TRS Group (n=26)		Healthy Controls (n=21)		Statistic: Mann-Whitney U Test			
	Min-Max	Median	Min-Max	Median	Z	r	U	p
0-back RTs	370.56 - 851.38	496.92	297.8 - 630.1	385.33	-3.659	1.87 [a]	102	p < .0005*
1-back RTs	372.78 - 912.00	519.78	340.2 - 638.2	444.44	-3.060	.45 [a]	130	p = .002*
2-back RTs	378.67 - 1204.63	615.72	402.6 - 760.9	546.71	-1.926	.28	183	p = .054
3-back RTs¬	332.43 - 1179.60	753.00	361.6 - 1067.8	642.11	-2.128	.03	166	p = .033*

* significant at p < 0.05, but note Bonferroni correction in this family of 4 multiple comparisons at p = 0.0125

¬ n=25: 0ne TRS participant who scored 0/9 in the 3-back condition was not included.

Cohen (1988): r =.10, .30 and .50 indicate small, medium and large effect sizes respectively.

3.6.2 Standard Deviations

A similar convergence to those observed for the RTs at higher levels of cognitive load emerged from a corresponding analysis for the standard deviations (SDs), shown in Table 3. 14 below. Consistent with the faster reaction times, standard deviations in the control group were smaller than in the TRS group in every condition. This difference was significant ($p < 0.05$) for the 0-back and 1-back conditions, although the latter would not survive Bonferroni correction with alpha = 0.0125, while the differences were non-significant at higher levels of cognitive load. Following Cohen (1988), examination of the

'r value' indicates a large effect size for the difference for the 0-back condition and a medium effect size for the 1-back, while the effect sizes were negligible and small for the 2- and 3-Back conditions respectively.

Table 3. 13 Comparison of Median Standard Deviations (ms) at each Level of Cognitive Load on the N-Back Task

Cognitive Load	TRS Group (n=26)		Healthy Controls (n=21)		Statistic: Mann-Whitney U Test			
	Min-Max	Median	Min-Max	Median	Z	r	U	p
0-back SDs	32.38 - 411.82	97.86	22.2 - 455.4	54.03	-3.402	0.50 [a]	114	p = .001*
1-back SDs	27.04 - 274.34	152.37	22.2 - 386.2	86.68	-2.290	0.33 [b]	166	p = .022*
2-back SDs	56.10 - 403.59	175.67	85.7 - 384.6	154.96	-.086	0.01	269	p = .932
3-back SDs ¬	56.09 - 436.85	228.68	69.8 - 448.5	202.85	-.673	0.10	232	p = .501

* significant at $p < 0.05$, but only the 0-Back comparison would survive Bonferroni correction in this family of 4 multiple comparisons at $p = 0.0125$
¬ n=25

Cohen (1988): r =.10, .30 and .50 indicate small, medium and large effect sizes respectively.

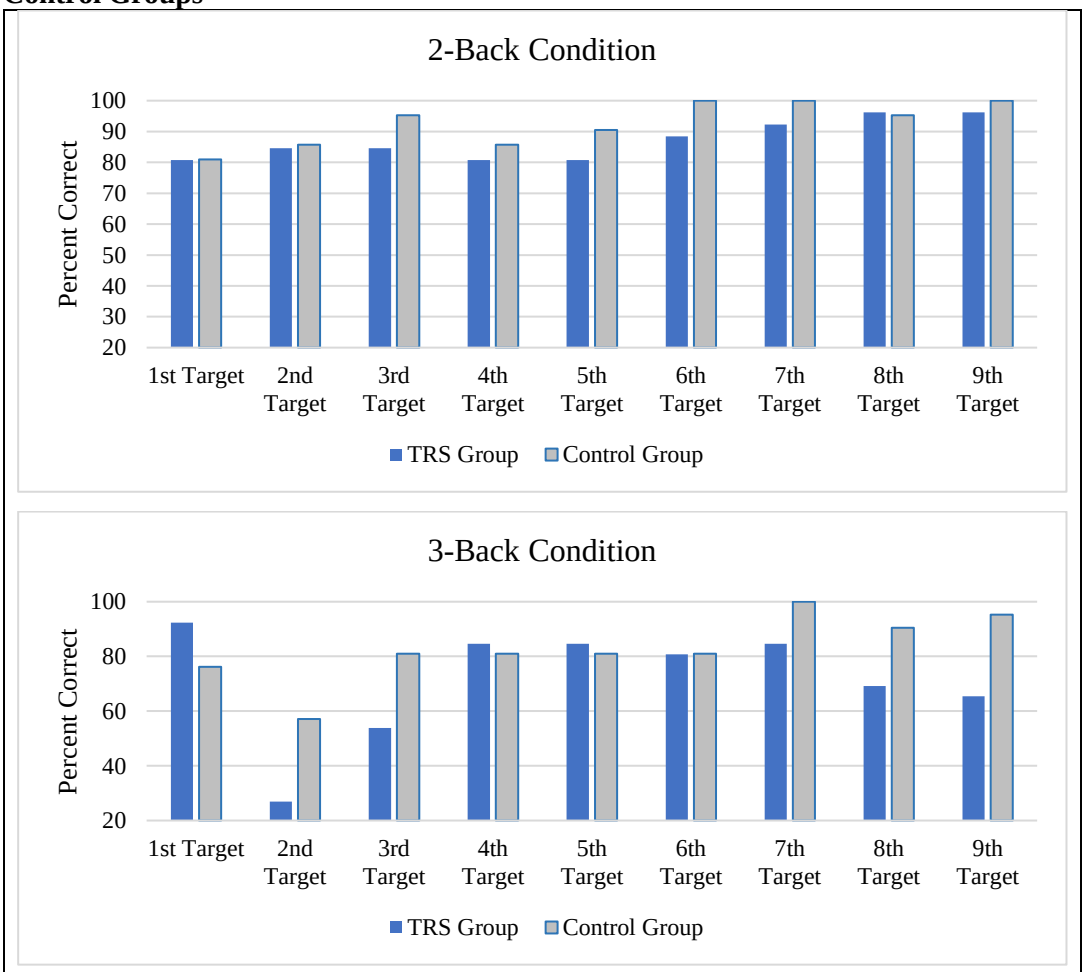
3.6.3 Target Accuracy and False Positive Responses

When it is considered there were 168 opportunities for an individual to make an error in the NBACK task (from 3 blocks of 14 stimuli for each of the four levels of cognitive load), overall target accuracy was high in both participant groups (96.47% for the TRS group and 98.07% for controls). However, when only responses to the 36 target stimuli were considered (omission errors), accuracy fell to 88.68% in the TRS group and 93.65% in the control group. A Mann-Whitney U test confirmed there was a significant difference in overall target accuracy between the TRS (Md = 88.89, n = 26) and controls groups (Md = 97.22, n = 21), U = 144.5, z = -2.775, p = .006, r = .4. Applying Cohen's (1988) criteria, the r value indicated a medium effect size.

However, when accuracy was assessed for each trial when a target was present, a more nuanced pattern emerged. Differences in target accuracy between the groups were negligible in the 0-Back and 1-Back conditions with target accuracy at 99.92% in the TRS group in each condition while only two errors were made across the entire control group; accordingly, Figure 3. 9 below only shows responses for the 2-Back and 3-Back conditions.

The following is merely descriptive however, it demonstrates target accuracy in the TRS group in the 2-Back condition was similar or lagged behind the control group only slightly. While in the 3-Back condition, responses to the first target in the series of nine were more

Figure 3. 9 Comparison of Correct Responses to Individual Targets by the TRS and Control Groups



% Correct	Block 1			Block 2			Block 3		
Target:	1st	2nd	3rd	4th	5th	6th	7th	8th	9th
TRS 2-Back	80.8	84.6	84.6	80.8	80.8	84.6	92.3	96.2	96.2
HC 2-Back	81.0	85.7	95.2	85.7	90.5	100.0	95.2	95.2	100.0
TRS 3-Back	92.3	26.9	53.8	84.6	84.6	80.8	84.6	69.2	65.4
HC 3-Back	76.2	57.1	81.0	81.0	81.0	81.0	100.0	90.5	95.2

accurate in the TRS group than in the control, but were markedly worse to the second, while the control group also faltered. Across the middle of the experiment (targets 4-6), accuracy in the TRS group was similar to that of the control group. However, it decreased to 69.2% and 65.4% for the last two targets. Overall, however, these rates demonstrate that not only could TRS participants perform the task at the highest level of cognitive load, but most were still demonstrating engagement at the end rather than giving up or responding randomly.

Also, accuracy levels overlapped considerably in the two groups, as 14/26 (53.9%) of TRS participants made 2 or fewer omissions errors out of a possible 9 during the 3-back condition, which compares with 16/21 (76.2%) control participants.[50]

Group differences in the rates of omission errors, were tested at each level of cognitive load and the results are shown in Table 3. 14. Significantly fewer omission errors were made by the control group compared to the TRS in the 0-back and 3-back conditions. These differences would not survive Bonferroni correction, but had medium effect sizes.

Table 3. 14 Comparison of the number of Omission Errors at each Level of Cognitive Load in the N-Back Task.

Cognitive Load	TRS Group (n=26)		Healthy Controls (n=21)		Statistic: Mann-Whitney U Test			
	Min-Max	Median	Min-Max	Median	z	r	U	p
0-Back Errors	0 -- 2	0	0 -- 0	0	-2.103	0.307 [b]	220.5	.035*
1-Back Errors	0 -- 3	0	0 -- 1	0	-1.181	0.172 [a]	243.5	.238
2-Back Errors	0 -- 5	0	0 -- 4	0	-.895	0.131 [a]	235.5	.371
3-Back Errors	0 -- 9	2	0 -- 6	0	-2.280	0.333 [b]	168.5	.023*

* significant at $p < 0.05$, but would not survive Bonferroni correction in this family of 4 multiple comparisons at $p = 0.0125$
Cohen (1988): r =.10, .30 and .50 indicate small, medium and large effect sizes respectively.

3.6.4 False Positive Errors

Many participants, 10/26 (39%) TRS and 13/21 (62%) controls made no false positive errors out of a possible 132 during the task. As can be seen in Table 3. 15, a significant group difference emerged only in the 3-Back condition, which had a medium effect size (r = .40). However, this difference appears to have been due to 3 TRS participants who accounted for half of the false positive errors (one in the higher PANSS group made 8 false positive errors, one lower and one higher PANSS participant made 7 false positive errors each). Figure 3. 10 shows the relative proportion of false positive errors to omissions after the scores of these participants were excluded and similar false positive rates between the groups.

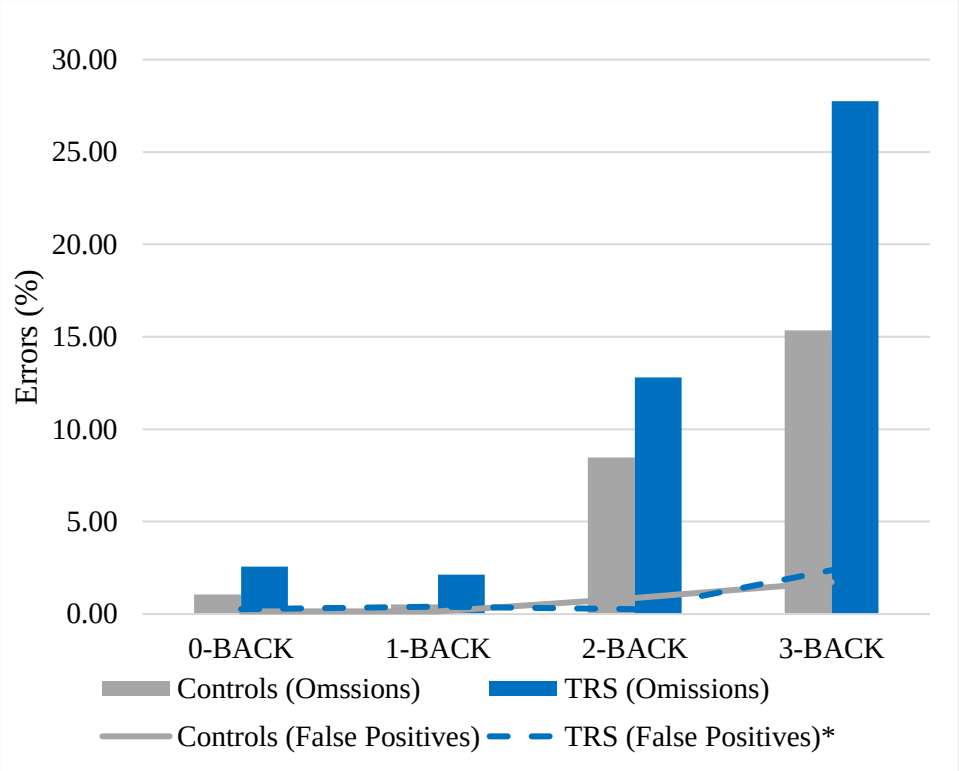
[50] Two TRS individuals (S17 and S24) made no omission errors during the experiment; one control almost did as well (S32) but made an omission error in the 1-back).

Table 3. 15 Comparison of Total Error (Omission and False Positives) at each Level of Cognitive Load in the N-Back Task.

Cognitive Load	TRS Group (n=26)		Healthy Controls (n=21)		Statistic: Mann-Whitney U Test			
	Min-Max	Median	Min-Max	Median	z	r	U	p
0-Back Errors	0 -- 2	0	0 -- 1	0	-1.246	0.182 [a]	235.0	.213
1-Back Errors	0 -- 3	0	0 -- 1	0	-1.892	0.276 [b]	204.0	.058
2-Back Errors	0 -- 5	0.5	0 -- 4	0	-.900	0.131 [a]	234.0	.368
3-Back Errors	0 -- 9	3.5	0 -- 7	1	-2.707	0.395 [b]	148.0	.007*

* significant at $p < 0.05$, also after with Bonferroni correction with alpha at 0.0125
Cohen (1988): r =.10, .30 and .50 indicate small, medium and large effect sizes respectively.

Figure 3. 10 Comparison of Omission and False Positive Errors made by TRS and Control Groups Across all Trials*



Percentage of Errors:	0-BACK	1-BACK	2-BACK	3-BACK
Controls (n = 21), Omission Errors	1.06	0.53	8.46	15.34
Controls (n = 21), False Positive Errors	0.14	0.14	0.86	1.73
TRS (n = 23*), Omission Errors	2.56	2.14	12.81	27.76
TRS (n = 23*), False Positive Errors	0.26	0.40	0.26	2.37

* Excludes 3 participants who contributed 23/46 false positives across the group.

3.6.5 On-line Behavioural Responses of the Lower and Higher PANSS Groups

As can be seen in Table 3. 16 below, there were no significant differences between the lower and higher PANSS groups for four behavioural variables obtained during the on-line neuroimaging across all levels of cognitive load. These were target accuracy, omission errors, false positive errors, omission and false positive errors combined. Nor was there a significant difference in mean reaction times during the 0-Back condition when omission error rates were 1.6% in the lower PANSS group and 4.6% in the higher PANSS group, a difference which was nonsignificant: (Md = 0, n =14) in the lower PANSS and (Md = 0, n=12) in the higher PANSS groups, U = 67, z = -1.192, p = .233, r = .23). However, mean standard deviations in the 0-Back condition for the higher PANSS group were significantly smaller in the lower PANSS group (with a medium to large effect size), indicating there was less variation in responding than by individuals in the higher PANSS group.

Table 3. 16 Behavioural Data Comparing Lower and Higher PANSS Groups

	TRS (n=26)	Lower PANSS (n=14)		Higher PANSS (n=12)		Statistic: Mann-Whitney U Test			
	Median (min-max)	Min-Max	Median	Min-Max	Median	z	r	U	p
Accuracy for Targets (N-Back %)	88.89 (66.68-100)	66.68-100	91.67	69.45–97.22	87.5	-1.408	0.276[b]	57	0.159
Omission Errors (N-Back, %)	11.11 (0- 33.33)	2.78 – 30.55	8.33	2.78-30.55	12.5	-1.408	0.276[b]	57	0.159
False Positive Errors (N-Back, %)	2.27 (0-18.18)	0.0 – 15.91	2.27	0.00–18.18	2.27	-1.407	0.276[b]	64.5	0.295
Total Errors (N-Back %)	10.71 (3.57-25)	3.57-23.2	8.93	3.57 - 25	11.61	-1.718	0.337[b]	51	0.086
Reaction Times (0-Back)	496.93 (370.56-851.38)	407.11 – 695.67	469.44	370.56 - 851.38	558.38	-1.646	0.061	52	0.100
Standard Deviations (0-Back)	97.86 (32.38 - 411.82)	32.38 - 316.95	85.33	48.33 – 411.82	147.58	-2.469	0.484[c]	36	0.014*

* $p < 0.05$ before correction. (Adjusted alpha for six comparisons = 0.008).
[b] = medium effect size; [c] = medium to large effect size. After Cohen (1988): r =.10, .30, .50 indicating small, medium and large effects.

3.7 Correlations between Symptoms, Cognitive and Behavioural Variables

3.7.1 Negative Symptoms and Variables associated with Attention

It was proposed that negative symptoms might be associated with attention so correlations were performed with scores on the CPT-IP and other putative markers of attention: 0-Back SDs and Omission Errors across all conditions of the n-back task. The latter might correlate with attention or cognitive control, since failures to respond might follow attentional lapses, a lack of volition or working memory deficits.

As can be seen in Table 3. 17 and the scatterplot in Figure 3. 11(a), there was a significant negative correlation between negative symptoms and 0-Back SDs, indicating that less variability in SDs was associated with fewer negative symptoms. A negative correlation between CPT-IP scores and negative symptoms was also significant, indicating that worse scores on this test of "sustained attention/vigilance" were associated with more negative symptoms (Figure 3. 11 (b). There was also a significant positive correlation between the percentage of omission errors in the n-back task (Figure 3. 11 (c) and negative symptoms. At first sight, these correlations appear to support the proposal that negative symptoms might be associated with decrements in attention.

Further correlations were performed between omission errors with 0-Back SDs and CPT-IP scores (Table 3. 17) which both might be described as having trend significance at $p = .061$ and $p = .063$ respectively. Their direction was congruent with the proposal that accuracy in the n-back might be associated with attention or cognitive control.

The series of related scatterplots (Figures 3.11 – 3.15) mark data points according to whether individual participants had a lower or higher level of negative symptoms. From these, it can be seen that scores for the correlations associated with a lower level of negative symptoms tend to cluster in the area related to better performance. However, this generalisation does not hold for negative symptoms and performance IQ (Figure 3. 13, c).

Table 3. 17 Inter-correlations between Variables Proposed to be Associated with Attention for the TRS group

Spearman's rho:		Negative Symptoms	Standard Deviations in 0-Back Condition	Continuous Performance Task (CPT-IP)	Percentage of Omission Errors (N-Back task)
Negative Symptoms	Correlation Coefficient	1.000			
	Sig. (2-tailed)	.			
	N	25			
Standard Deviations in 0-Back Condition	Correlation Coefficient	.741***	1.000		
	Sig. (2-tailed)	.001	.		
	N	25	26		
Continuous Performance Task (CPT-IP)	Correlation Coefficient	-.564**	-.417*	1.000	
	Sig. (2-tailed)	.006	.048	.	
	N	22	23	23	
Percentage of Omission Errors in the N-Back task (to 36 targets)	Correlation Coefficient	.431*	.372	-.394	1.000
	Sig. (2-tailed)	.032	.061	.063	.
	N	25	26	23	26

* Correlation is significant at the 0.05 level.
** Correlation is significant at the 0.001 level.
*** Correlation would survive Bonferroni correction (with alpha for 24 comparisons = .002, Tables 3.18, 3.19).

- Scatterplots for negative symptoms and "attentional" variables in Table 3. 17

Figure 3. 11 Correlations between Negative Symptoms and Attention (SDs in the 0-Back condition, CPT-IP scores, and N-Back Omission Errors)

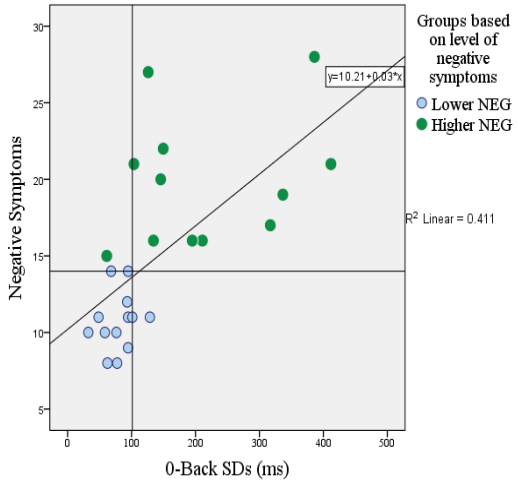
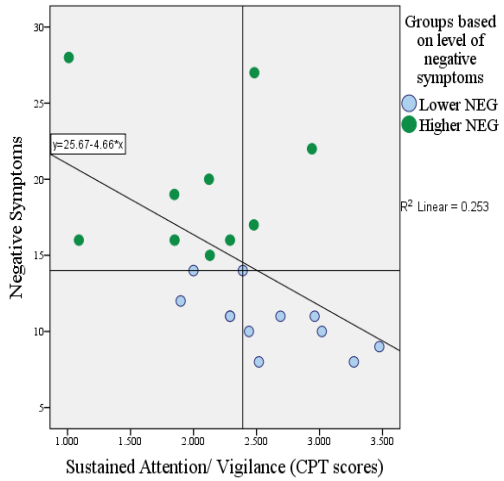
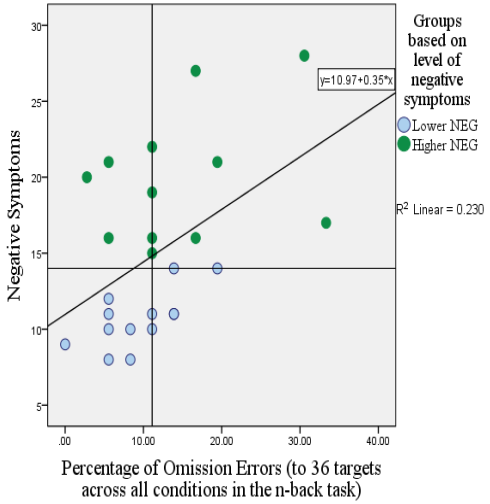
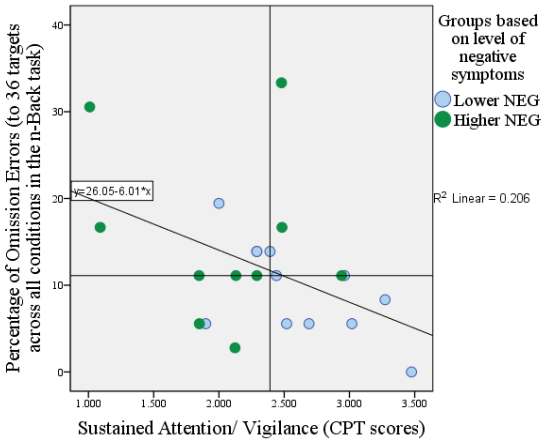
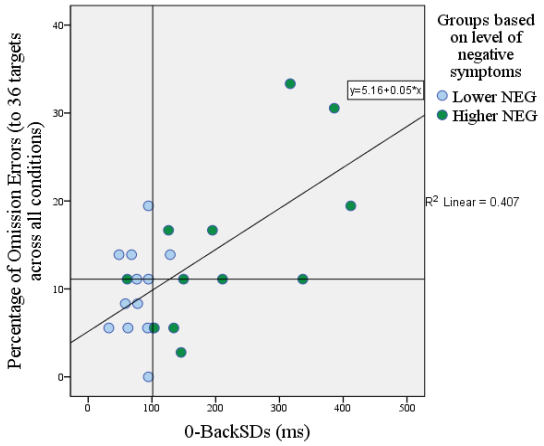
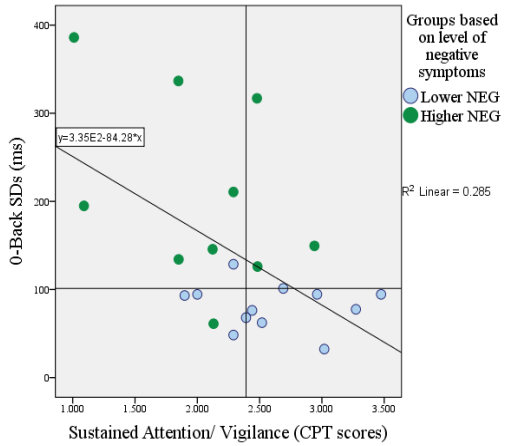
a) Correlation between Negative Symptoms and 0-Back Standard Deviations	**b) Correlation betweeen Negative Symptoms and Continuous Performance Task Scores**	**c) Correlation between Negative Symptoms and N-Back Omission Errors**
		
Vertical line indicates median of 0-Back SD's at 101.21ms. Horizontal line indicates median score of negative symptoms at 14.	Vertical line indicates median score on the CPT = 2.391. Higher scores indicate better performance. Horizontal line indicates median score of negative symptoms at 14.	Vertical line indicates median of N-Back omission errors at 11.11%. Horizontal line indicates median score of negative symptoms at 14.
rho = .741, n=25, p = .001	rho = -.564, n=22, p = .006	rho = .431, n=25, p = .032

Figure 3. 12 Inter-correlations between CPT-IP scores and Attention (Standard Deviations in the 0-Back condition and Omission Errors in the N-Back task)

a) Correlation between Percentage of Omission Errors and CPT-IP Scores	b) Correlation between Percentage of Omission Errors and 0-Back SDs	c) Correlation between CPT-IP Scores and 0-Back SDs
		
Vertical line median CPT score at 2.391. Horizontal line indicates median of omission errors in the N-Back task at 11.11%.	Vertical line indicates median of 0-Back SDs at 101.21ms. Horizontal line indicates median of omission errors in the N-Back task at 11.11%.	Vertical line indicates median CPT score at 2.391. Horizontal line indicates median of 0-Back SDs at 101.21ms.
rho = -.394, n=23, p = .063	rho = .372, n=26, p = .061	rho = -.417, n=23, p = .048

3.7.2 Negative Symptoms and Estimated IQ

Table 3. 18 shows significant negative correlations between FIQ and negative symptoms, and between VIQ and negative symptoms. However, the correlation between PIQ and negative symptoms was not significant. This pattern was repeated when the 0-Back SDs were substituted for negative symptoms in correlations with estimated IQ scores. When CPT-IP scores were substituted, a similar pattern emerged. Scatterplots accompanying Table 3. 18 concerning the IQ variables are shown in Figure 3. 13 for correlations with negative symptoms; Figure 3. 14 for correlations with 0-Back SD scores and Figure 3. 15 for correlations with the CPT-IP scores.

Table 3. 18 Correlations between Variables associated with Attention and WASI Scores including Subscale Asymmetry

Spearman's rho (except where ¬ indicates Pearson).		Negative Symptoms	Standard Deviations in 0-Back Condition	Continuous Performance Task	Full-scale IQ	Verbal IQ	Performance IQ	Asymmetry between IQ subscales
Full-scale IQ	Correlation Coefficient	-.416*	-.461*	.543**¬	1.000			
	Sig. (2-tailed)	.043	.021	.007	.			
	N	24	25	23	25			
Verbal IQ	Correlation Coefficient	-.500**	-.512**	.546**¬	.905***¬	1.000		
	Sig. (2-tailed)	.013	.009	.007	.001	.		
	N	24	25	23	25	25		
Performance IQ subscale	Correlation Coefficient	-.153	-.244	.315¬	.838***¬	.532**¬	1.000	
	Sig. (2-tailed)	.476	.240	.143	.001	.006	.	
	N	24	25	23	25	25	25	
IQ Asymmetry	Correlation Coefficient	-.514**	-.450**	.237	.281	.576**	-.202	1.000
	Sig. (2-tailed)	.010	.024	.276	.174	.003	.333	.
	N	24	25	23	25	25	25	25

* Correlation is significant at the 0.05 level.

** Correlation is significant at the 0.01 level.

*** would survive Bonferroni correction with an alpha = .0021 for 24 comparisons.

¬ indicates use of the Pearson product moment correlation

Note: Cohen (1988, pp. 79-81) proposed the strength of a correlation coefficient is small if it is between .10 and .29, medium if it is between .30 and .49 and large if it is between .5 and 1.0.

- Scatterplots for negative symptoms and estimates of IQ in Table 3. 18

Figure 3. 13 Correlations between Negative Symptoms and Estimated Full-Scale IQ and Subscales as measured on the WASI

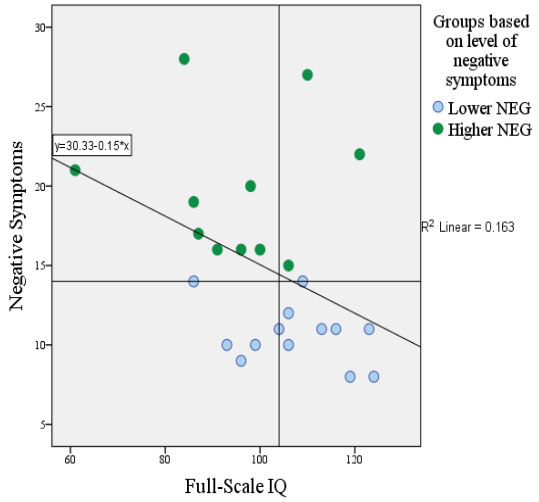
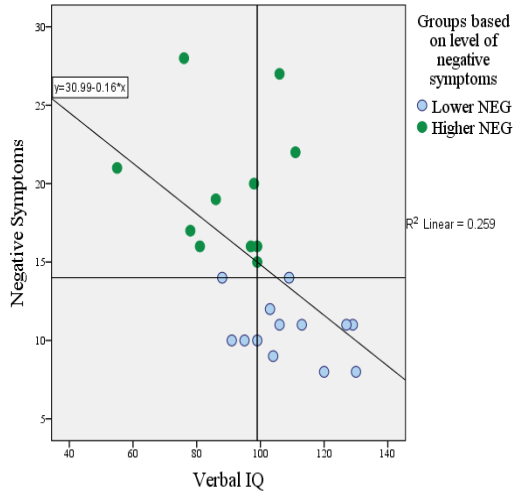
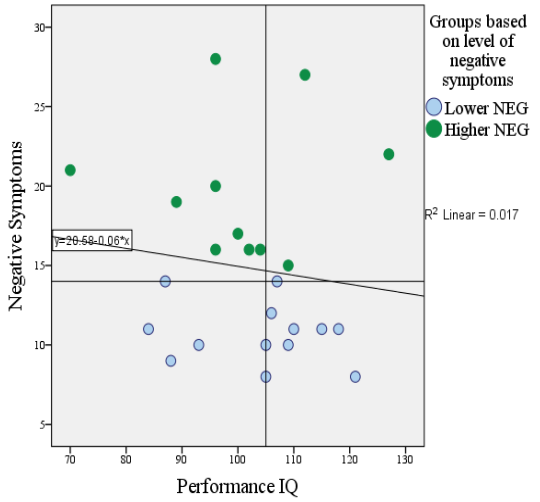
a) Correlation between Negative Symptoms and Full-Scale IQ	**b) Correlation between Negative Symptoms and Verbal IQ**	**c) Correlation between Negative Symptoms and Performance IQ**
		
Vertical line indicates median FIQ score at 104. Horizontal line indicates median negative symptoms score at 14.	Vertical line indicates median standard VIQ score at 99. Horizontal line indicates median negative symptoms score at 14.	Vertical line indicates median standard PIQ score at 105. Horizontal line indicates median negative symptoms score at 14.
rho = -.416, n=24, p = .043	rho = -.500, n=24, p = .013	rho = -.153, n=24, p = .476

Figure 3. 14 Correlations between Estimated IQ Standard Scores and SDs in the 0-Back Condition of the N-Back Task.

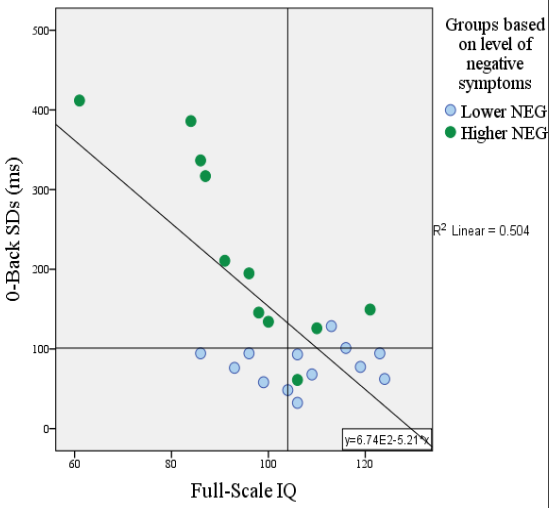
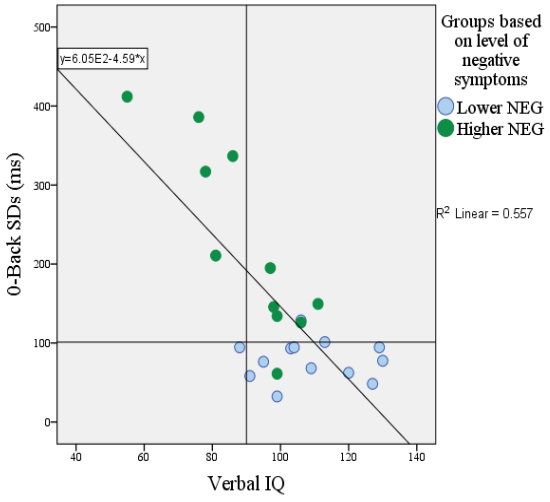
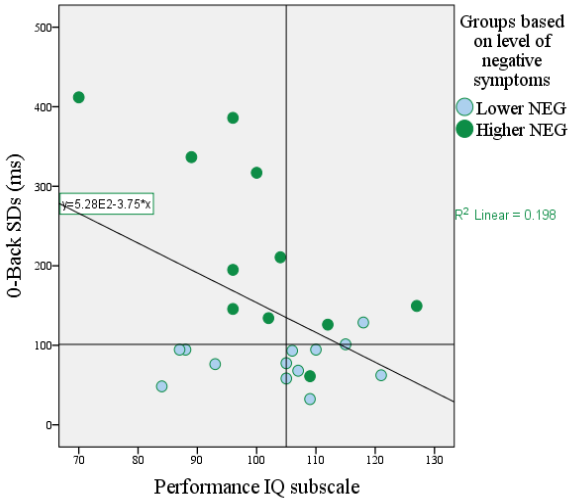
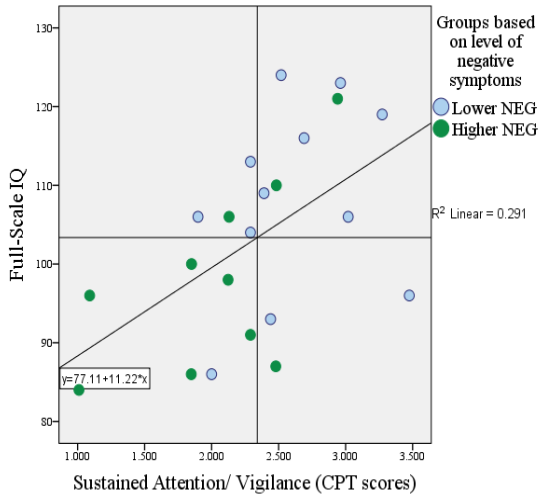
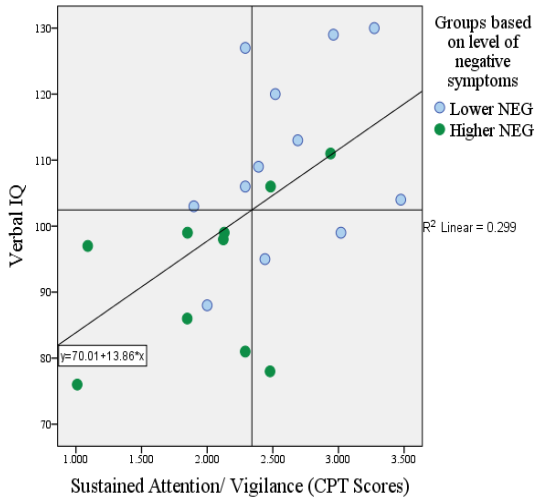
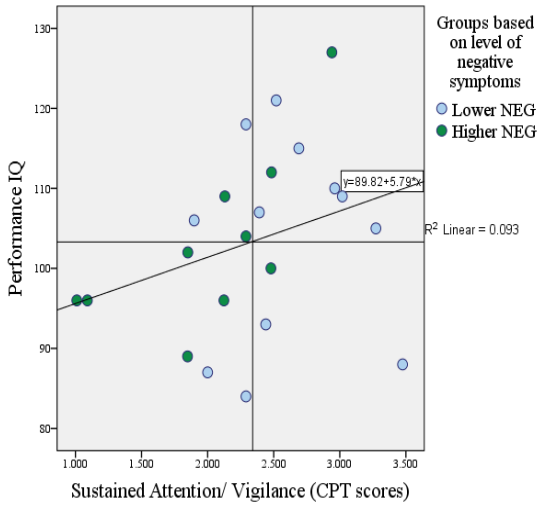
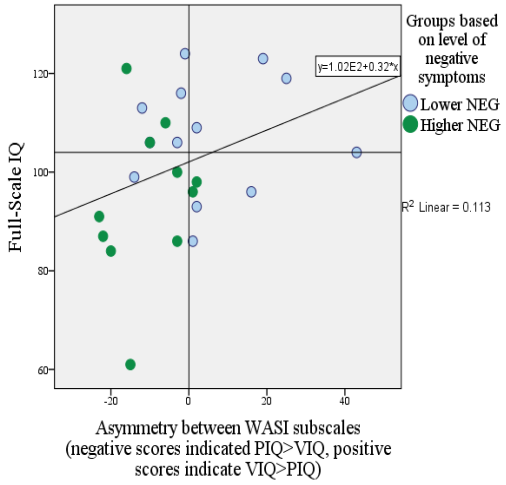
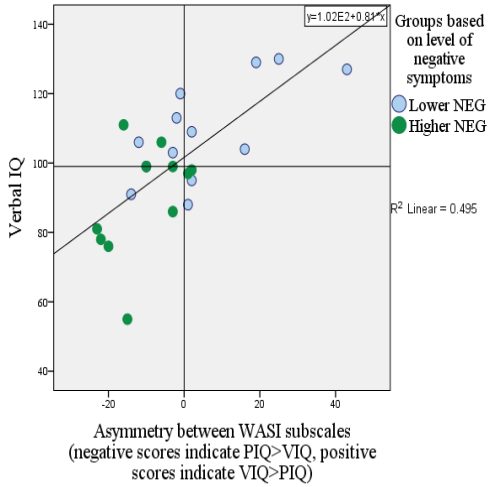
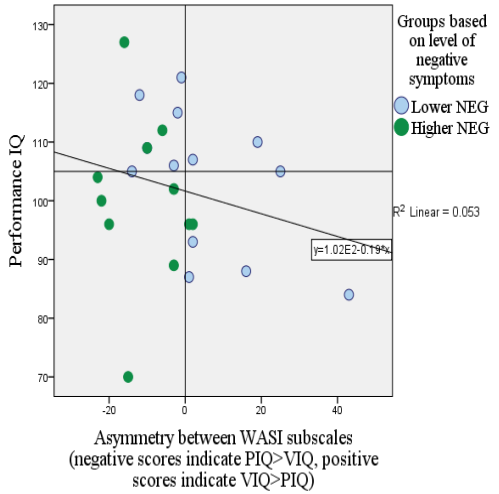
a) Correlation between Full-scale IQ and 0-Back SDs	b) Correlation between Verbal IQ and 0-Back SDs	c) Correlation between Performance IQ and 0-Back SDs
		
Vertical line indicates the median of FIQ standard scores at 104. Horizontal line indicates median of individual mean SDs scores in the 0-Back at 101.21ms.	Vertical line indicates the median of Verbal IQ standard scores at 99. Horizontal line indicates median of individual mean SDs scores in the 0-Back at 101.21ms.	Vertical line indicates the median of Performance IQ at 105. Horizontal line indicates median of individual mean SDs scores in the 0-Back at 101.21ms.
rho = -.461, n=25, p = .021	rho = -.512, n=25, p = .009	rho = -.244, n=25, p = .240

Figure 3. 15 Correlations between Estimated IQ Standard Scores and Performance on the Continuous Performance Task (MCCB)

a) Correlation between Full-scale IQ and CPT-IP Scores	b) Correlation between Verbal IQ and CPT-IP Scores	c) Correlation between Performance IQ and CPT-IP Scores
		
Vertical line indicates mean CPT score at 2.34. Horizontal line indicates mean Full-scale IQ at 103.	Vertical line indicates mean CPT score at 2.34. Horizontal line indicates mean Verbal IQ at 102.5	Vertical line indicates mean CPT score at 2.34. Horizontal line indicates mean PIQ at 103.
r = .543, n=23, p = .007	r = .546, n=23, p = .007	r = .315, n=23, p = .143

- Scatterplots concerning asymmetry between the WASI subscales and estimated IQ in Table 3. 18

Figure 3. 16 Correlations involving Asymmetry between WASI subscales and estimated IQ Scores

(a) Full-scale IQ and Asymmetry between WASI subscales	(b) Verbal IQ and Asymmetry between WASI subscales	(c) Performance IQ and Asymmetry between WASI subscales
		
rho = .281, n=25, p = .174	rho = .576, n=25, p = .003	rho = -.202, n=25, p = -.333

Note: in all of these plots the four data points on the right side represent individuals in the superior VIQ group.

3.7.3 Correlations concerning asymmetry between the WASI subscales

The final row of Table 3. 18 reports the correlations with the IQ Asymmetry variable which is the difference between participants' individual scores on the VIQ and PIQ subscales (where positive scores indicate higher VIQ scores and negative scores indicate higher PIQ scores). This was generated because in section 3.3 substantial differences between the WASI subscales were reported affecting 52% of the TRS group raising concerns that the small VIQ>PIQ subgrouping might represent a confound in the data, particularly as they were distinctive in other respects.

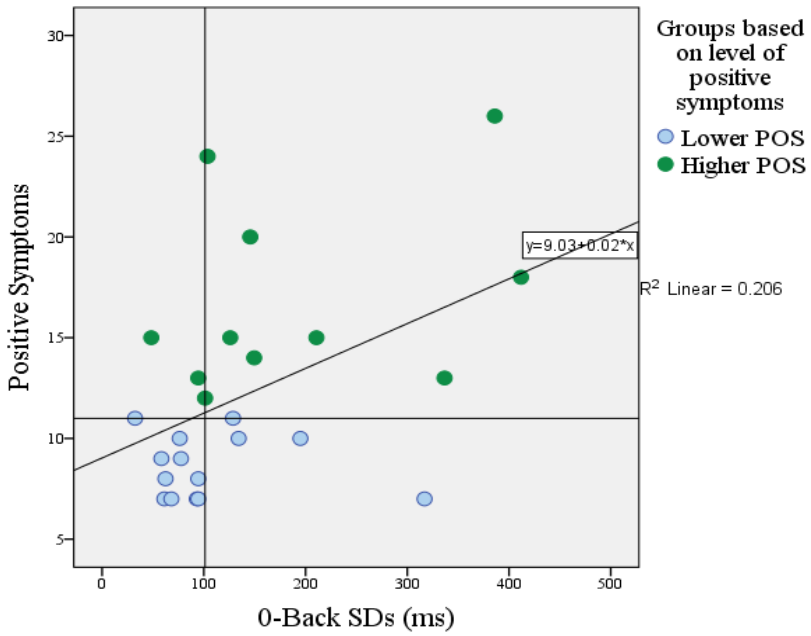
Of note, in correlations between IQ Asymmetry and other "attentional" variables, there was a correlation with negative symptoms indicating VIQ>PIQ scores were associated with fewer negative symptoms. However, a correlation in the same direction, between total PANSS scores and IQ Asymmetry (not shown in the table) did not reach significance (rho = -.348, n = 25, p = .089). There was also a significant correlation between IQ Asymmetry and 0-Back SDs , but not with CPT-IP scores. There was a correlation between IQ Asymmetry and VIQ (again, favouring the VIQ>PIQ individuals), however, the correlations with PIQ and FIQ were not significant. The corresponding scatterplots for correlations with asymmetry are shown in Figure 3. 16.

3.7.4 Correlations with Positive Symptoms

Not every individual with a higher level of negative symptoms also had more positive symptoms: three participants had positive symptom scores above the median for positive symptoms and negative symptom scores below the median for negative symptoms; while four participants showed the opposite pattern. However, there was strong positive correlation between negative and positive symptoms: rho = .595, n=25, p = .002. Another correlation was conducted between positive symptoms and RTs in the 0-Back condition in case higher scores might be associated with arousal but this was non-significant (rho = .327 n=25, p = .111).

Further correlations were conducted between positive symptoms and the same seven variables as for negative symptoms in sections 3.7.1, 3.7.2. However, none approached significance apart from one between positive symptoms and 0-Back SDs, in Figure 3. 17.

Figure 3. 17 Correlation between positive symptoms and 0-Back SDs



Vertical line indicates median of 0-Back SDs at 101.21ms
Horizontal line indicates the median score of positive symptoms at 11 (the minimum score for positive symptoms is 7). Scores of 12 and above are indicated as "Higher POS" in the scatterplot. Bonferroni for 8 correlations with positive symptoms alpha = .006

rho = .457, n=25, p = .022

Considered alongside the corresponding correlation for negative symptoms, this scatterplot confirms lower symptom scores were associated with lower SDs in the 0-Back condition.

3.7.5 Post Hoc Analyses based on a Reduced Set of Participants without the Superior VIQ Grouping (VIQ>PIQ)

The four individuals exhibiting intellectual asymmetry were distinguished in other ways:

Table 3. 19 Distinctive Characteristics of Individuals with Higher VIQ than PIQ

- Distinguished by their rarity, only 16% of the TRS group had superior estimated verbal IQ scores relative to performance IQ scores.
- VIQ>PIQ individuals had low negative symptom scores (mean = 9.75, SD: 1.5, 8-11, n=4). Seven indicates no pathology, also see "floor effect" in Figure 3. 3.
- The mean difference between the VIQ and PIQ subscales was marked at 22 standard points (Table 3. 6).
- Median estimated FIQ was higher in the VIQ>PIQ grouping (111.5 compared to 103 in the no asymmetry grouping and 99 in PIQ>VIQ grouping).
- They progressed to a trial of clozapine more quickly than most TRS individuals in this study (mean = 2.5 years, SD=2.18, 1-5, n=4 compared with mean = 7.7 years, SD=5.3, 0.5-21, n=22).
- Mean standard deviations in the 0-Back condition at 78.71ms (SD: 21.78) were highly similar to those in the control group at 79.74ms (SD: 91.20).
- Mean RTs in the 0-Back condition at 469.66ms were intermediate between the control and reduced TRS groups at 412.66ms and 540.54ms respectively.
- While error rates increased with increasing load, VIQ>PIQ participants exhibited a lower percentage of omission errors than the control group at higher levels of cognitive load in the 2-Back and 3-Back conditions (Figure Appx. 5. 3).
- As depicted in Figure Appx. 5. 2, RTs for VIQ>PIQ participants increased sharply in the 3-Back condition, along with standard deviations, to approximate and exceed those for the TRS group, even though error rates were lower.
- The median MCCB profile for VIQ>PIQ participants differed markedly from other TRS. Performance on category fluency and the CPT-IP exceeded the 50th percentile (Figure Appx. 5. 1). However, performance on planning and reasoning (NAB Mazes) was depressed, consistent with lower PIQ/fluid intelligence scores.
- Social cognition was superior with a median score at the 21st percentile compared to the rest of the TRS group at 2.4.
- Visual learning and verbal learning scores were superior, although the latter seemed low in the context of average to good VIQ scores. Behaviourally, none recalled any item from the last three positions upon first recall of the HVLT-R list (Table Appx. 4. 1).

Consequently, as described in Methods (at the end of section 2.7.1) some of the correlational analyses (shown in Tables 3.17 and 3.18) were repeated in a reduced set which excluded scores from VIQ>PIQ participants and are reported in corresponding tables in Appendix 5 (Table Appx. 5. 1 and Table Appx. 5. 2). The correlations mostly survived the exclusion of 4 participants, however, the highly significant correlation between negative symptoms and CPT-IP scores was abolished. This was arguably restored (with modest significance) after an outlier was removed (Figure Appx. 5. 4). The inverse correlation between 0-Back SDs and CPT-IP also remained moderately significant. In addition, the highly significant inverse correlation between negative symptoms and the proposed proxy for sustained attention (0-Back SDs) was not weakened in the reduced set, while the positive correlation between 0-Back SDs and the percentage of omission errors in the n-back task as a whole assumed significance having been at trend in the full set.

In contrast to most of the attentional variables, the removal of the four VIQ>PIQ individuals abolished the significant correlations between negative symptoms and FIQ and VIQ, while the correlation between negative symptoms and PIQ remained nonsignificant. Also, the correlation between CPT-IP and VIQ scores was markedly less significant. In this reduced set, however, the previously non-significant correlation between PIQ and CPT-IP performance became highly significant ($r = .586$, $n=19$, $p = .008$).

Associations between the MCCB and estimated IQ scores in the full and reduced sets are reported in Table Appx. 5. 4. The colour coding of significance levels in that table highlights that little changed in the reduced set. Notable exceptions concern the weakening of correlations to "trend" levels between VIQ and visual learning, also between VIQ and category fluency. While the previously nonsignificant correlation between reasoning and problem solving (NAB Mazes) and PIQ, and between Trail Making and PIQ become significant. As both variables are likely correlates of fluid intelligence, this may be consistent with the newly significant correlation between CPT-IP and PIQ (above), after the removal of 4 PIQ scores which were markedly depressed relative to VIQ scores.

Results Part: II Functional MRI

3.8 Functional MRI Results of the N-Back Verbal Working Memory Task

As described in section 2.12, it is worth restating that unlike many other approaches, significant contrasts observed with XBAM methodology do not require adjustment for multiple comparisons because it compares the statistical significance of the median SSQ values for the group at each voxel by permutation sampling against a null distribution generated from the randomised time series. This is an important advantage.

The main effect of the task, defined as progressive linear increases and decreases in the haemodynamic response with increasing cognitive load in the TRS and control groups separately will be shown in the following section. In addition, Appendix 2 contains tables showing significant within-group changes in the haemodynamic response relative to baseline at each level of cognitive load (as opposed to linear changes reported in the trend analyses, i.e. 1-back vs. 2-back vs. 3-back).

3.9 Trend Analysis

It was hypothesised there would be linear increases and decreases in the haemodynamic response with increasing cognitive load in a fronto-parietal network that is usually engaged by the verbal n-back task. However, as this study is largely exploratory, further predictions were not made. The statistical activation maps for the positive and negative linear trends are shown in Table 3. 20 and Table 3. 21 for the control group and Table 3. 22 and Table 3. 23 for the TRS group. There were 21 significant clusters for each group with respect to areas exhibiting a positive linear trend, while 11 significant clusters of relative decreases in the haemodynamic response/ "deactivations" were observed in each table reporting a negative linear trend.

- Description of Positive Linear Trends

As can be seen from Tables 3.21 and 3.23 below for the control and TRS groups respectively, there were significant linear trend increases in the haemodynamic response associated with increasing cognitive load (1-Back < 2-Back < 3-Back) across 21 brain areas including several loci, bilaterally, in the prefrontal cortex (BA9 and BA10 in both groups, extending to the right BA8 in the TRS group). Linear trend increases were also observed in parietal cortex in both groups, notably the left inferior parietal lobe in the TRS group and bilaterally in the control group; however, in the TRS group there were moderate large

clusters with peak loci in the right precuneus (BA19, cluster size 95mm^3) and left precuneus (BA 7, cluster size 207mm^3,with the peak medially), while there was a large area of activation only in left precuneus (BA19, cluster size 364mm^3) in the control group, although the peak was described as being 10mm away). Bilateral activations were observed in the cerebellum, however, in the control group these involved the posterior lobe (left 173mm^3, right 32mm^3), while in the TRS group, peak loci were ascribed to the anterior lobe (left 124mm^3, right 109mm^3).

There was a significant cluster of 80 mm^3 in the left posterior cingulate (BA30) in the control group which was not present in the TRS group. Another difference concerned a large cluster of 240 mm^3, anteriorly, in the left claustrum for the control group which was not observed in the TRS group; also, in the control group, the thalamus, bilaterally (186mm^3 in the left hemisphere and, more specifically, in the right hemisphere, the ventral anterior nucleus, cluster size 202mm^3). These exhibited linear trend increases. Further, there was a linear trend increase in the middle temporal gyrus, (left BA21, right BA20 at 186mm^3 and 231mm^3 respectively) in the control group which was not present in the TRS group.

On the other hand, there appeared to be linear trend increases in areas associated with visual processing in the TRS group (left fusiform gyrus, BA36, 44mm^3 and right cuneus, BA19, 28mm^3) which were not present in the control group. Another difference concerned a linear trend increase in the left caudate (cluster size 75 mm^3), which was present in the TRS group but absent in the control group.

- Description of Negative Linear Trends

Tables 3.22 and 3.24 list a smaller number of areas (11 in each group) exhibiting significant decreases in the haemodynamic response relative to group baselines as cognitive load increased in the control and TRS groups respectively.

As might be expected, in these tables, structures associated with the default mode network are more prominent in the negative trend analyses. In particular, there was a large cluster of 455mm^3 in the left medial frontal gyrus (BA10) in the control group which was also proximal to sizeable cluster of 550mm^3 in the left superior frontal gyrus (BA 9) which had a peak co-ordinate in a medial position. While, in the TRS group, the corresponding activation was much more circumscribed at 122mm^3 in the left medial frontal gyrus albeit with a different Brodmann label (BA8). There were also proximal areas exhibiting trend deactivation not seen in the control group in the left middle frontal gyrus (BA8, 110mm^3)

and large cluster posteriorly, with a peak medially, in the cingulate gyrus (left BA24, cluster size 708mm^3) which raises the possibility these areas might have performed a similar function or compensatory function to that observed in the control group.

More posteriorly in the control group, a very large cluster of deactivation of 1704mm^3 was observed in the parietal lobe with a peak medially in the left paracentral lobule (BA31); also, one of 643mm^3 in the left postcentral gyrus (BA3). In the TRS group, there was a sizeable cluster of 615mm^3 in the cingulate gyrus (BA31) in the right hemisphere, along with clusters of 382mm^3 the right precuneus (BA 7) and 262mm^3 in right posterior cingulate (BA30). Linear trend decreases were not observed in the right hemisphere for these last three areas in the control group.

However, linear trend decreases were observed in both groups in the occipital lobe: in the left cuneus, BA23 medially (262mm^3) and right middle occipital gyrus BA18 (85mm^3) in the control group and in the right cuneus, BA17 medially (197mm^3) in the TRS group.

More laterally, linear trend decreases were also observed in both groups in the precentral gyrus, in the right BA44 (135 mm^3) in the control group and in the left BA6 (51mm^3) and left BA4 (736 mm^3) in the TRS group.

Both groups also showed linear trend decreases in the right transverse temporal gyrus (BA41) in sizeable clusters of 585mm^3 and 393mm^3 in the control and TRS groups respectively. However, bilateral linear trend increases in the middle temporal gyrus (right BA20 (231mm^3), left BA21 (186mm^3), left BA39 (454mm^3) and trend decreases in the left middle temporal gyrus BA21 (193mm^3) and the right superior temporal gyrus, BA38 (102 mm^3) were only observed in the control group.

Finally, the control group exhibited a linear trend increase in the right insula (BA13, 270mm^3) and a decrease in the left insula, (BA13, 442mm^3), while a trend decrease was not was not observed in the TRS group. However, a linear trend increase was observed in the right insula (BA13, 270mm^3) with a peak at an identical set of co-ordinates (Talairach = 33, 22, 10), along with another cluster in the left insula BA13 in a homologous cluster (213mm^3, Talairach = -29, 19, 7).

3.9.1 Trend Analysis within the Control Group

Table 3. 20 Within Control Group: areas exhibiting a significant positive linear trend in activity with increasing cognitive load

Anatomical Location	Brodmann Area	Hemis-phere	Cluster size (mm^3)	p-Value	Talairach co-ordinates*		
					x	y	z
Superior Frontal Gyrus	BA 10	R	311	0.00292	-36	56	13
Middle Frontal Gyrus (6 mm away)	BA 10	L	405	0.00289	-31	48	9
Middle Frontal Gyrus	BA 9	R	330	0.00193	40	33	33
Middle Frontal Gyrus	BA 9	L	355	0.00271	-36	22	33
Insula	BA 13	R	270	0.00241	33	22	10
Claustrum	-	L	240	0.00194	-25	22	6
Medial Frontal Gyrus	BA 6	R	341	0.00049	0	11	46
Inferior Frontal Gyrus (5.2 mm away)	BA 9	R	132	0.00733	46	10	29
Frontal Lobe, Sub-Gyral	BA 6	R	422	0.00020	25	0	53
Frontal Lobe, Sub-Gyral,	BA 6	L	369	0.00064	-25	0	53
Thalamus, Ventral Anterior Nucleus	-	R	202	0.00702	11	-4	7
Thalamus	-	L	186	0.00792	-11	-4	-3
Middle Temporal Gyrus 5.2 mm away	BA 21	L	186	0.00931	-51	-30	0
Middle Temporal Gyrus	BA 20	R	231	0.00827	54	-41	-13
Inferior Parietal Lobe	BA 40	L	153	0.00176	-40	-48	40
Inferior Parietal Lobe	BA 40	R	389	0.00056	36	-48	40
Cerebellum, Posterior Lobe, Cerebellar Tonsil	-	L	173	0.00782	-33	-56	-33
Middle Temporal Gyrus (6.0 mm away)	BA 39	L	454	0.00120	-33	-57	27
Precuneus, (10.0 mm away)	BA 19	L	364	0.00265	-31	-62	39
Cerebellum, Posterior Lobe, Uvula	-	R	32	0.01167	4	-70	-30
Posterior Cingulate	BA 30	L	80	0.00376	-29	-70	13

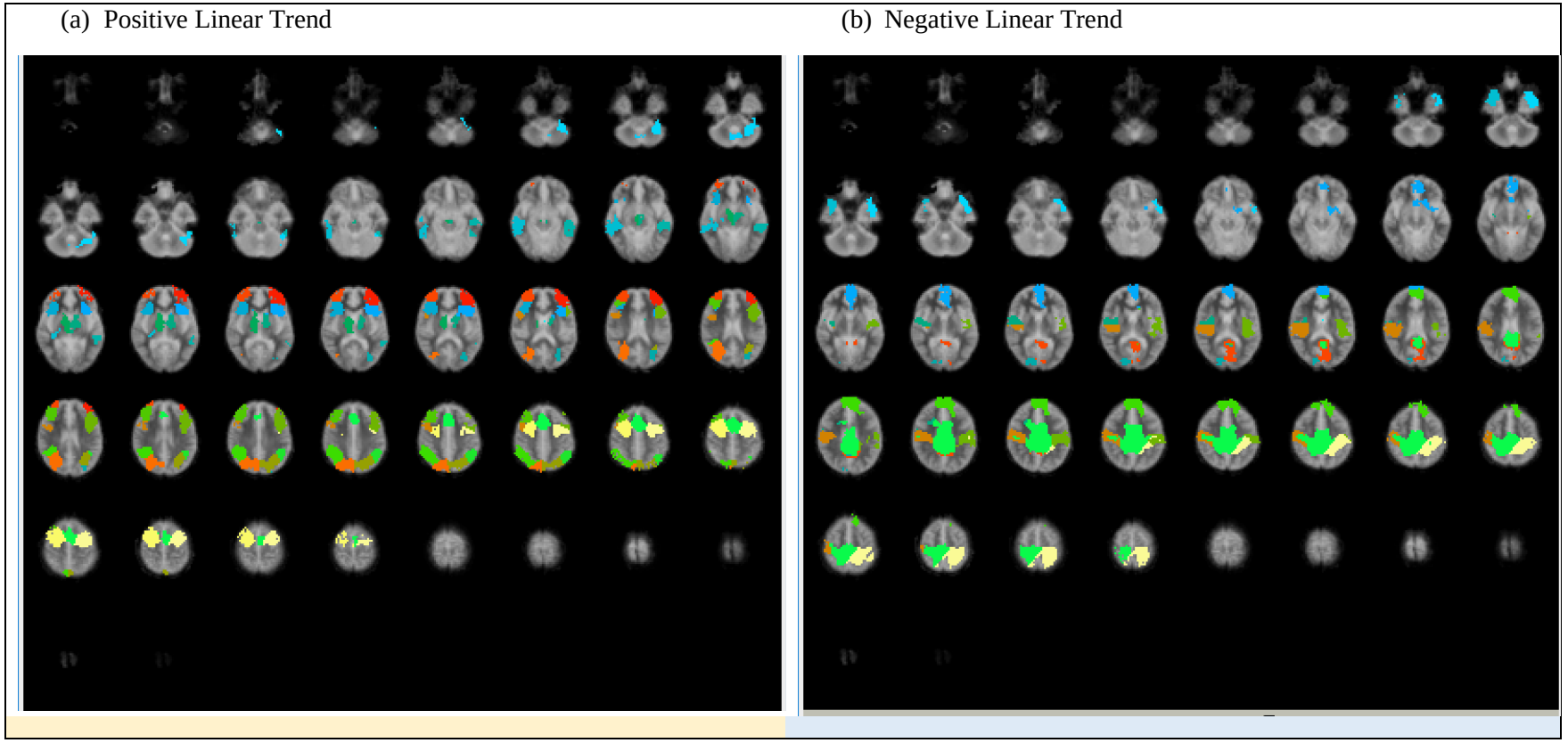
21 clusters ordered from an anterior to posterior in the coronal plane.
Age was used as covariate; voxel-wise p-value = <0.05, cluster-wise p= 0.02.

Table 3. 21 Within Control Group: areas exhibiting a significant negative linear trend in activity with increasing cognitive load.

Anatomical Location	Brodmann Area	Hemis-phere	Cluster size (mm^3)	p-Value	Talairach co-ordinates* x	y	z
Medial Frontal Gyrus	BA 10	L	455	0.00495	-4	59	7
Superior Frontal Gyrus	BA 9	L	550	0.00138	-4	52	30
Superior Temporal Gyrus	BA 38	R	102	0.00727	36	7	-30
Middle Temporal Gyrus	BA 21	L	193	0.00635	-43	0	-30
Precentral Gyrus, Frontal	BA 44	R	135	0.00505	51	0	7
Insula	BA 13	L	442	0.00493	-36	-14	14
Paracentral Lobule	BA 31	L	1704	0.00033	-4	-15	43
Transverse Temporal Gyrus	BA 41	R	585	0.00191	51	-19	13
Postcentral Gyrus, Parietal	BA 3	L	643	0.00185	-22	-30	59
Cuneus, Occipital Lobe	BA 23	L	262	0.00984	-4	-74	13
Middle Occipital Gyrus	BA 18	R	85	0.00938	18	-85	13

11 clusters ordered from an anterior to posterior in the coronal plane.
Age was used as covariate; voxel-wise p-value = <0.05, cluster-wise p= 0.02.

Figure 3. 18 Brain areas showing significant changes in the haemodynamic response with increasing cognitive load in the Control Group: (a) Positive Linear Trend and (b) Negative Linear Trend



3.9.2 Trend Analysis within the TRS Group

Table 3. 22 Within TRS Group: areas exhibiting a significant positive linear trend in activity with increasing cognitive load

Anatomical Location	Brodmann Area	Hemis-phere	Cluster size (mm^3)	p-Value	Talairach co-ordinates* x	y	z
Middle Frontal Gyrus	BA 10	R	183	0.00166	25	56	10
Middle Frontal Gyrus	BA 10	L	236	0.00115	-36	48	13
Middle Frontal Gyrus	BA 9	R	180	0.00195	36	33	33
Middle Frontal Gyrus	BA 9	L	153	0.00216	-40	30	30
Superior Frontal Gyrus	BA 8	R	40	0.00898	25	26	50
Insula, Sub-lobar	BA 13	R	199	0.00274	33	22	10
Caudate	-	L	75	0.00546	-31	21	9
Insula	BA 13	L	213	0.00269	-29	19	7
Medial Frontal Gyrus	BA 6	L	259	0.00031	0	15	43
Middle Frontal Gyrus (5.2 mm away)	BA 9	R	116	0.00276	50	14	26
Middle Frontal Gyrus	BA 6	R	204	0.00079	33	4	50
Precentral Gyrus	BA 6	L	135	0.00391	-36	0	30
Frontal Lobe, Sub-Gyral (5.2 mm away)	BA 6	L	264	0.00128	-19	-1	53
Supramarginal Gyrus (6.9 mm away)	BA 40	R	133	0.00232	44	-44	34
Fusiform Gyrus, Temporal Lobe	BA 36	L	44	0.01083	-51	-45	-20
Inferior Parietal Lobe	BA 40	L	291	0.00341	-44	-48	36
Cerebellum, Anterior Lobe	-	L	124	0.00512	-30	-52	-30
Cerebellum, Anterior Lobe, Culmen	-	R	109	0.00698	22	-56	-26
Precuneus	BA 19	R	95	0.00599	33	-67	40
Precuneus	BA 7	L	207	0.00515	-4	-70	43
Cuneus, Occipital Lobe	BA 19	R	28	0.00735	4	-89	33

21 clusters ordered from anterior to posterior in the coronal plane.
Age was used as covariate; voxel-wise p-value = <0.05, cluster-wise p= 0.01.

Table 3. 23 Within TRS Group: areas exhibiting a significant negative linear trend in activity with increasing cognitive load

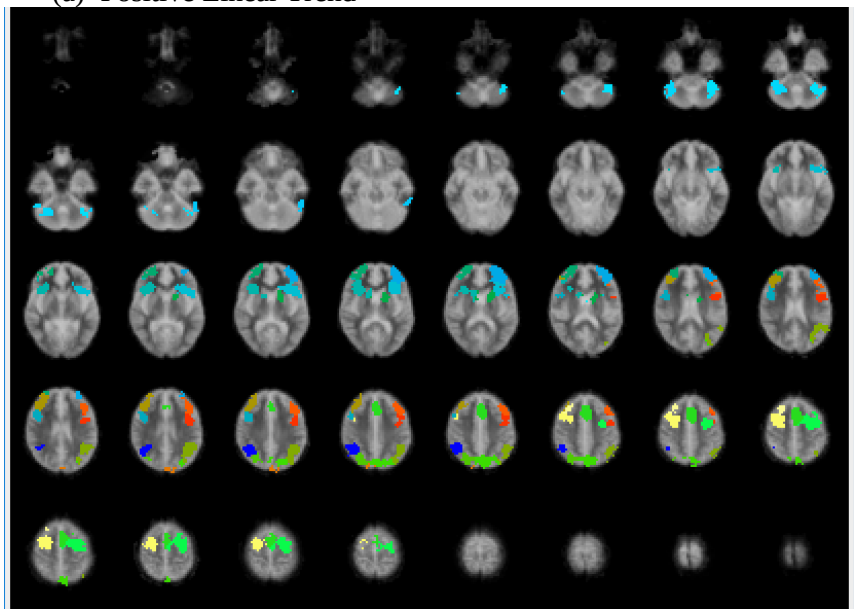
Anatomical Location	Brodmann Area	Hemis-phere	Cluster size (mm^3)	p-Value	Talairach co-ordinates* x	y	z
Precentral Gyrus, Frontal	BA 4	R	450	0.00249	43	-15	36
Medial Frontal Gyrus	BA 8	L	122	0.00751	-7	38	40
Middle Frontal Gyrus	BA 8	L	110	0.00598	-20	27	38
Precentral Gyrus (6.4 mm away)	BA 6	L	51	0.00707	-61	0	36
Cingulate Gyrus	BA 24	L	708	0.00077	-4	-15	40
Precentral Gyrus, Frontal (5.7 mm away)	BA 4	L	736	0.00225	-36	-20	40
Transverse Temporal Gyrus	BA 41	R	393	0.00819	36	-26	10
Cingulate Gyrus	BA 31	R	615	0.00137	20	-28	38
Precuneus	BA 7	R	382	0.00361	14	-44	53
Posterior Cingulate	BA 30	R	262	0.00818	18	-67	7
Cuneus, Occipital Lobe	BA 17	R	197	0.01166	4	-81	7

11 clusters ordered from an anterior to posterior in the coronal plane.
Age was used as covariate; voxel-wise p-value = <0.05, cluster-wise p= 0.01.

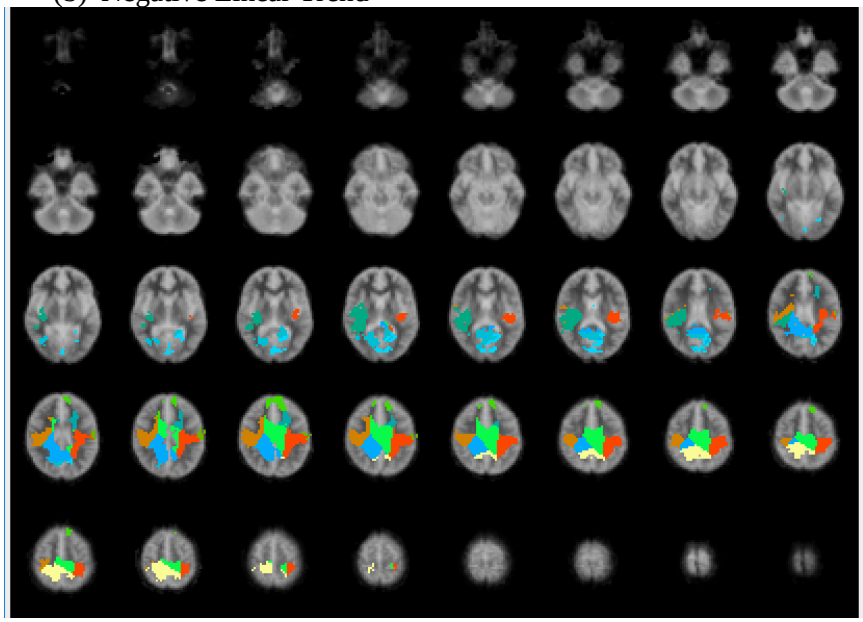
- *Statistical Maps*

Figure 3. 19 Brain areas showing significant changes in the haemodynamic response with increasing cognitive load in the TRS Group: (a) Positive Linear Trend and (b) Negative Linear Trend

(a) Positive Linear Trend



(b) Negative Linear Trend



3.10 Factorial Analysis Comparing TRS and Control Groups

- *The initial ANCOVA results*

After adjusting the thresholds to minimise the risk of type one error and repeating the analysis, the result of the initial ANCOVA between the TRS and control groups, indicated 5 clusters of significant differential activation. The peak co-ordinates for these were in the left medial frontal gyrus (BA 8), right frontal lobe sub-gyral (BA 6), left posterior cingulate (BA 31) nearest grey 6.9mm away, and right precuneus (BA 7) in the parietal lobe and left lingual gyrus in the occipital lobe. These were all highly significant - the cluster for the lingual gyrus was the least significant at $p = 0.007$. However, the clusters in the medial frontal gyrus and precuneus were very large at 815 and 997 voxels respectively.

Therefore, a more stringent analysis was conducted by raising the voxel p-value to 0.01 (from a default value at 0.5). This had the desired effect of reducing cluster sizes and demonstrated the "robustness" of the clusters that were still significant. However, the lingual gyrus was no longer significant which highlighted the risk of type 2 error had been increased. (This exploratory analysis is supplied for reference in Appendix 3).

- *The main ANCOVA results declustered*

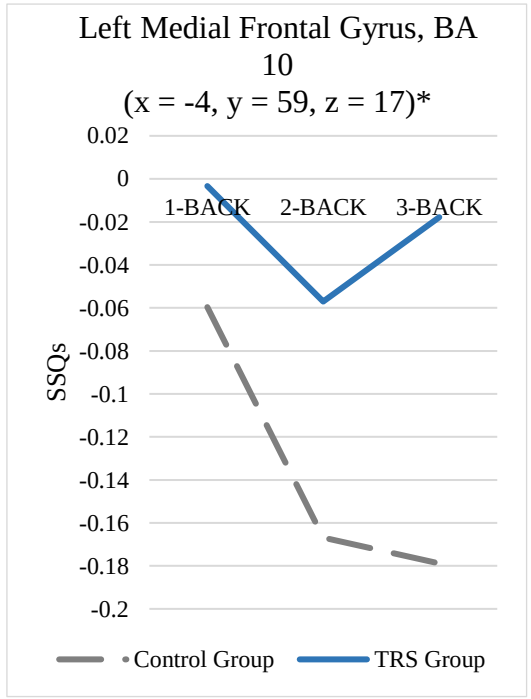
For the factorial analyses, interpretation of the figures in the following pages is helped considerably by the presence of a consistent pattern that emerges with increasing levels of cognitive load: namely, an attenuation in the increases and decreases in the haemodynamic response relative to group baselines in the TRS group relative to controls. A similar pattern is observed in the higher PANSS group compared to the lower PANSS group (section 3.11), thereby indicating the haemodynamic response is influenced by the level of pathology. This over-arching pattern in the factorial analyses was without exception: in no instances were greater increases or decreases observed in the group with a higher level of pathology.

Table 3. 24 Factorial Analysis comparing TRS Participants with Controls across Three Levels of Cognitive Load in the Working Memory Task

Anatomical Location	Brodmann Area	Hemis-phere	Cluster size (mm^3)	p-Value	Talairach co-ordinates* x	y	z
Medial Frontal Gyrus	BA 10	L	305	0.00309	-4	59	17
Medial Frontal Gyrus	BA 8	L	226	0.00370	-4	52	40
Superior Frontal Gyrus	BA 10	L	12	0.01208	-25	48	26
Anterior Cingulate	BA 24	L	159	0.01301	-7	30	-3
Superior Frontal Gyrus	BA 6	L	85	0.00718	-7	30	56
Middle Frontal Gyrus	BA 9	R	87	0.00897	43	19	33
Putamen	-	R	16	0.01239	22	19	-7
Superior Frontal Gyrus	BA 6	L	119	0.00437	0	4	50
Frontal Lobe, Sub-Gyral	BA 6	L	109	0.00386	-25	4	53
Frontal Lobe, Sub-Gyral	BA 6	R	245	0.00463	29	0	53
Thalamus	-	R	128	0.01084	11	-4	3
Cingulate Gyrus	BA 24	L	172	0.00375	-4	-15	33
Parahippocampal Gyrus (nearest grey 5.8 mm away)	BA 36	R	176	0.01237	40	-30	-11
Cingulate Gyrus (nearest grey 6.9mm away)	BA 31	L	285	0.00448	-3	-26	37
Middle Temporal Gyrus	BA 21	L	78	0.01211	-47	-33	0
Parietal Lobe, Sub-Gyral	BA 40	R	302	0.00505	36	-44	33
Paracentral Lobule	BA 5	L	56	0.01385	-10	-44	59
Limbic Lobe, Sub-Gyral (nearest grey 9.4mm away)	BA 31	L	174	0.00869	-19	-46	37
Parahippocampal Gyrus	BA 30	L	57	0.01404	-29	-48	3
Precuneus	BA 7	R	365	0.00721	22	-59	26
Lingual Gyrus	-	L	78	0.01211	-29	-70	0

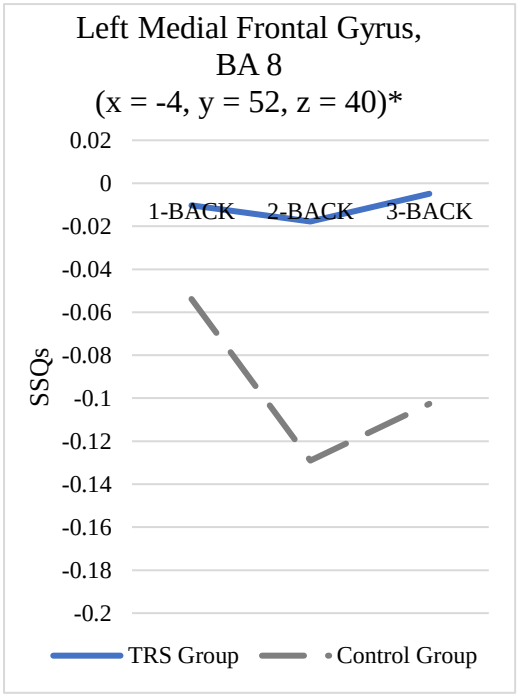
21 areas ordered from anterior to posterior in the coronal plane.
Age was used as covariate; voxel-wise p-value = <0.05, cluster-wise p= 0.01.
One participant was excluded from analyses for the 3-back condition as they scored 0/9 targets (minimum score permitted 6/9 correct responses).

Figure 3. 20 Haemodynamic response as cognitive load increased in TRS participants and controls in the left Medial Frontal Gyrus (BA 8 and BA 10) and the left Superior Frontal Gyrus (BA 6)



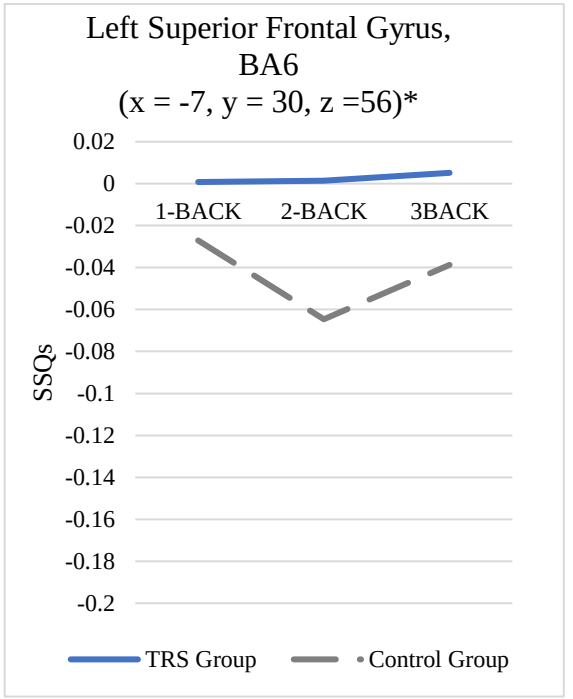
	1-Back	2-Back	3-Back
TRS Group	-0.00339	-0.05707	-0.01786
Control Group	-0.5967	-0.16682	-0.17887

* Significant at p = 0.00309



	1-Back	2-Back	3-Back
TRS Group	-0.01032	-0.01778	-0.00489
Control Group	-0.05385	-0.12902	-0.10256

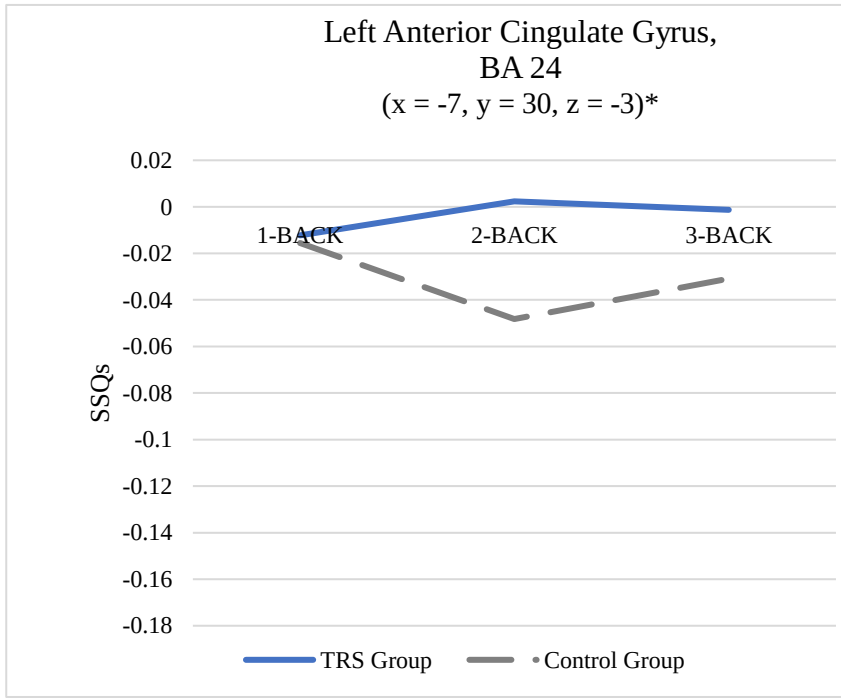
* Significant at p = 0.00370



	1-Back	2-Back	3-Back
TRS Group	0.00077	0.00134	0.00514
Control Group	-0.02709	-0.06465	-0.03873

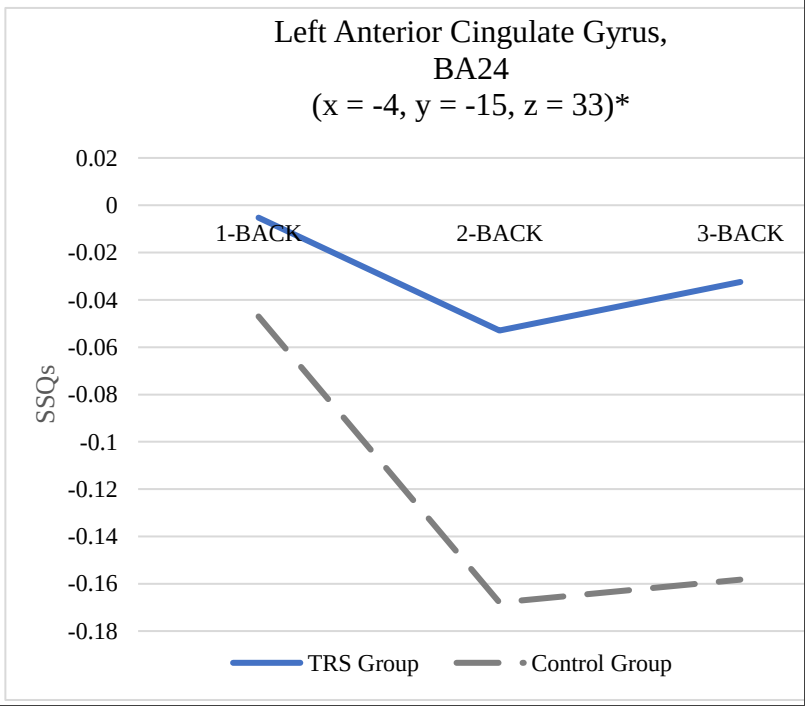
* Significant at p = 0.00718

Figure 3. 21 Haemodynamic response as cognitive load increased in TRS participants and controls in the left Anterior Cingulate Gyrus (BA 24)



	1-Back	2-Back	3-Back
TRS Group	-0.01225	0.00236	-0.00130
Control Group	-0.01554	-0.04821	-0.03087

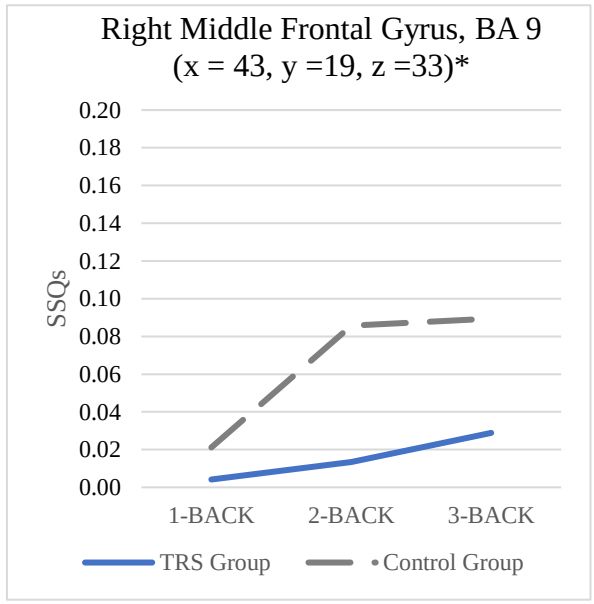
* Significant at p = 0.01301

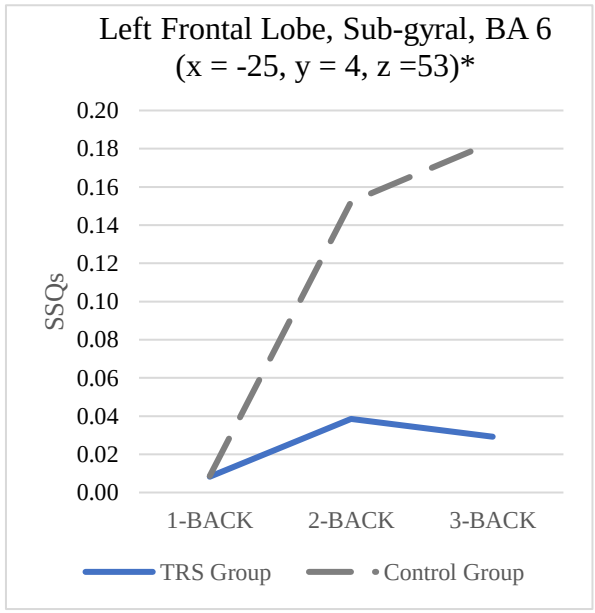


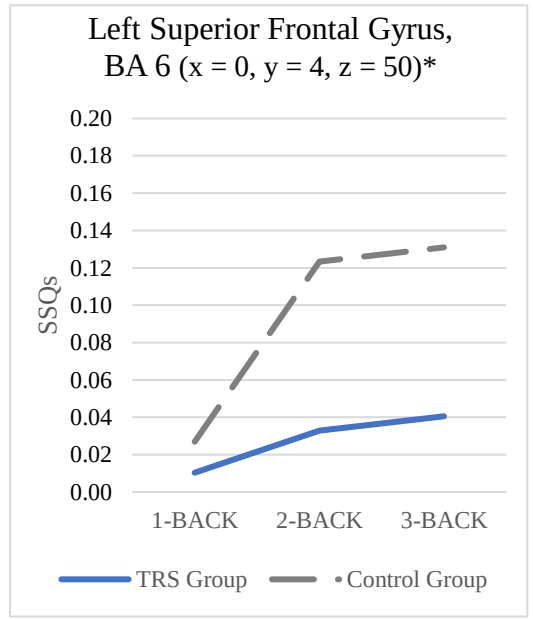
	1-Back	2-Back	3-Back
TRS Group	-0.00525	-0.05296	-0.03237
Control Group	-0.04701	-0.16794	-0.15823

* Significant at p = 0.00375

Figure 3. 22 Haemodynamic response as cognitive load increased in TRS participants and controls in the right Middle and left Superior Frontal Gyri (BA 9 and BA 6)





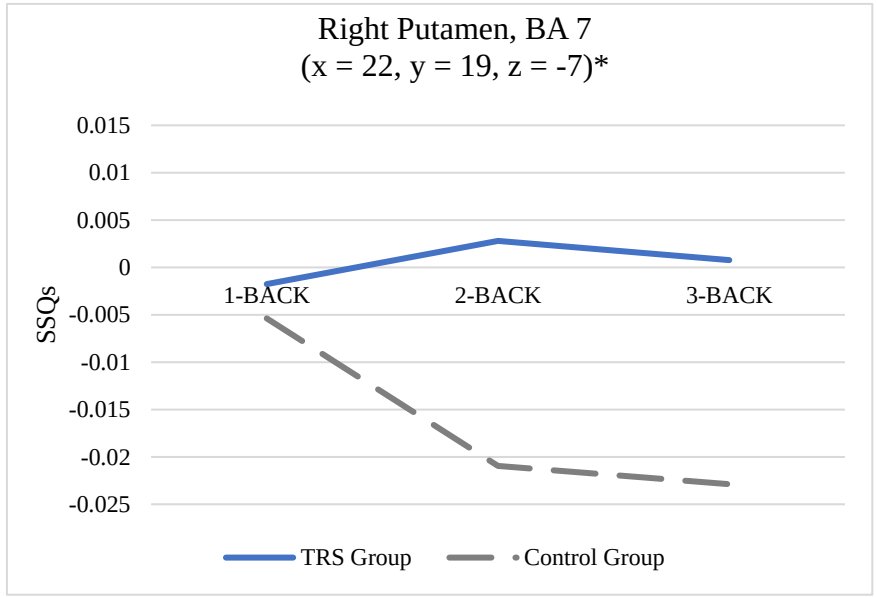


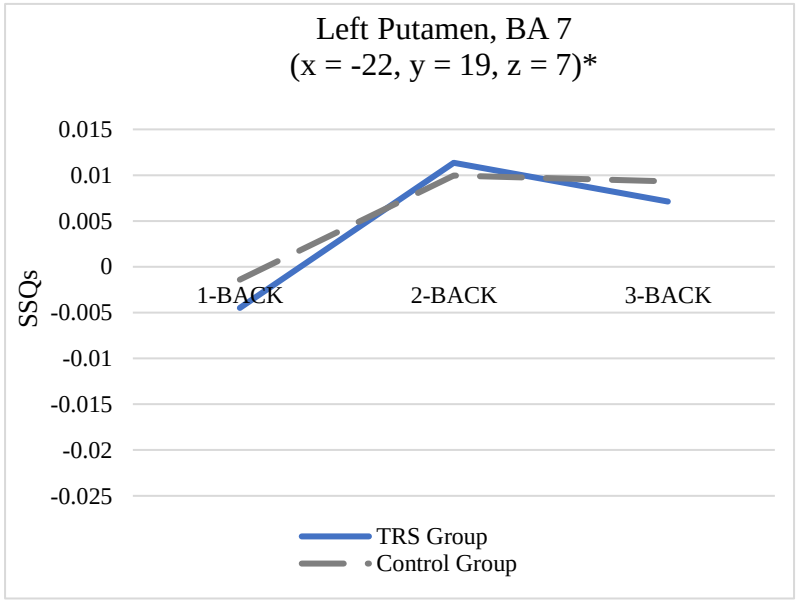
	1-Back	2-Back	3-Back
TRS Group	0.02116	0.08567	0.08944
Control Group	0.00416	0.01338	0.02886
* Significant at p = 0.00897			

	1-Back	2-Back	3-Back
TRS Group	0.00866	0.15219	0.18339
Control Group	0.00830	0.03853	0.02927
* Significant at p = 0.00386			

	1-Back	2-Back	3-Back
TRS Group	0.01033	0.03278	0.04052
Control Group	0.02692	0.12342	0.13098
* Significant at p = 0.00437			

Figure 3. 23 Haemodynamic response as cognitive load increased in TRS participants and controls in the right and left Putamen, BA 7

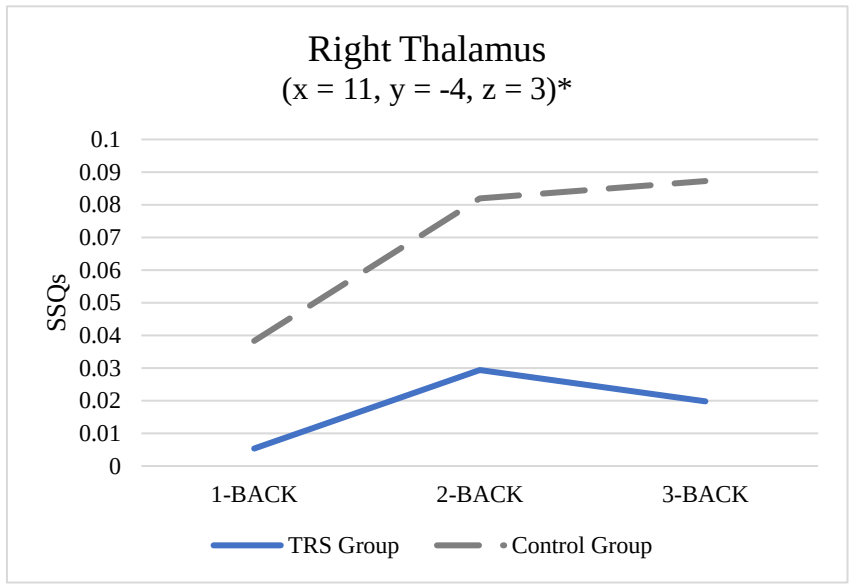


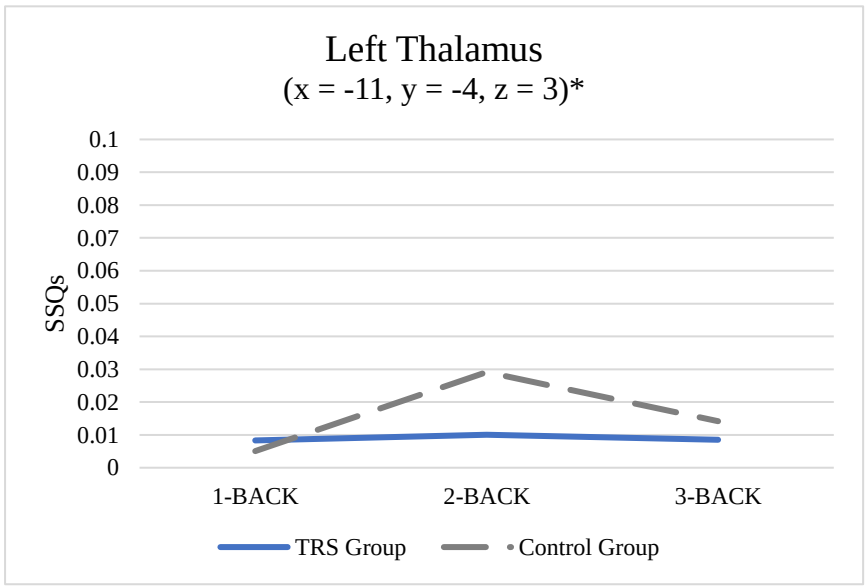


	1-Back	2-Back	3-Back
Control Group	-0.00176	0.00280	0.00076
TRS Group	-0.00538	-0.02095	-0.02288
* Significant at p = 0.01239			

	1-Back	2-Back	3-Back
Control Group	-0.00449	0.01135	0.00711
TRS Group	-0.00140	0.00996	0.00931
* Not significant - shown for comparison at contralateral co-ordinates			

Figure 3. 24 Haemodynamic response as cognitive load increased in TRS participants and controls in the right and left Thalamus

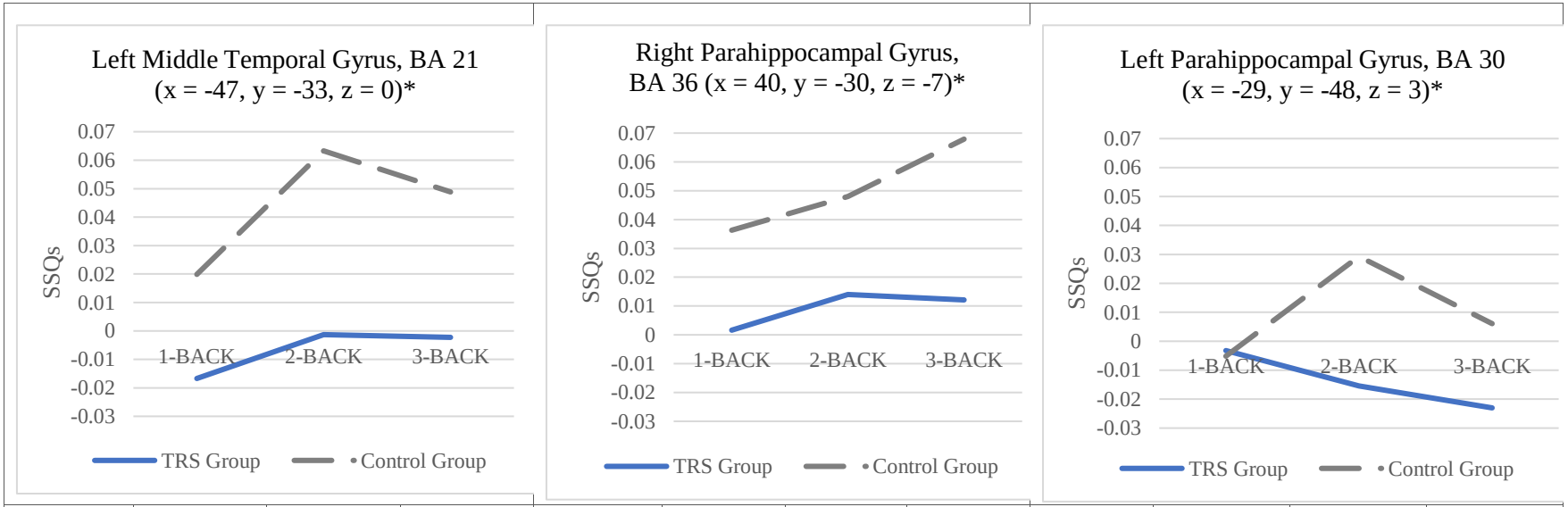




	1-Back	2-Back	3-Back
Control Group	0.03831	0.08190	0.08725
TRS Group	0.00535	0.02939	0.01978
* Significant at p = 0.01084			

	1-Back	2-Back	3-Back
Control Group	0.00832	0.01005	0.00849
TRS Group	0.00507	0.02913	0.01416
* Not significant - shown for comparison at contralateral co-ordinates			

Figure 3. 25 Haemodynamic response as cognitive load increased in TRS participants and controls in the Parahippocampal Gyrus bilaterally (BA 36 and BA 30) and the left Middle Temporal Gyrus (BA 21)

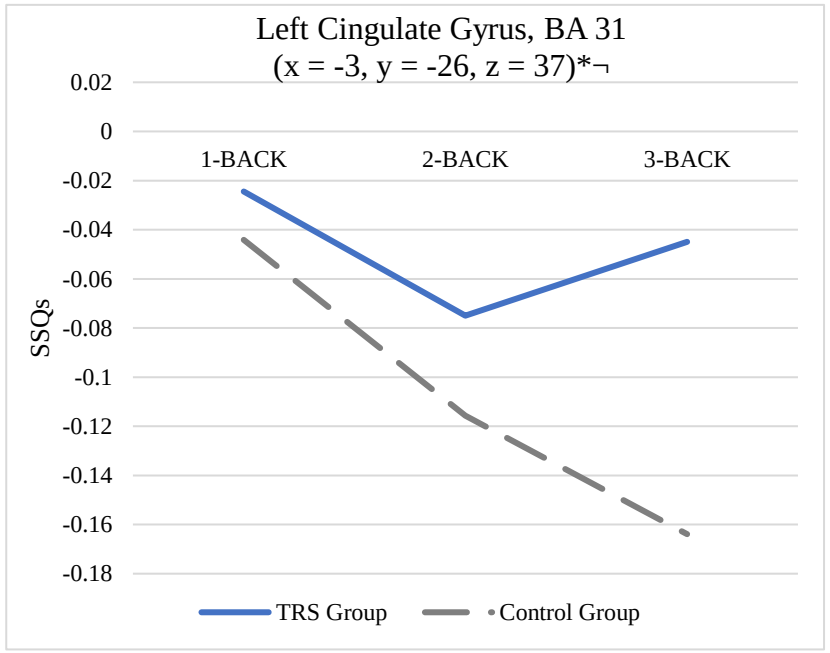


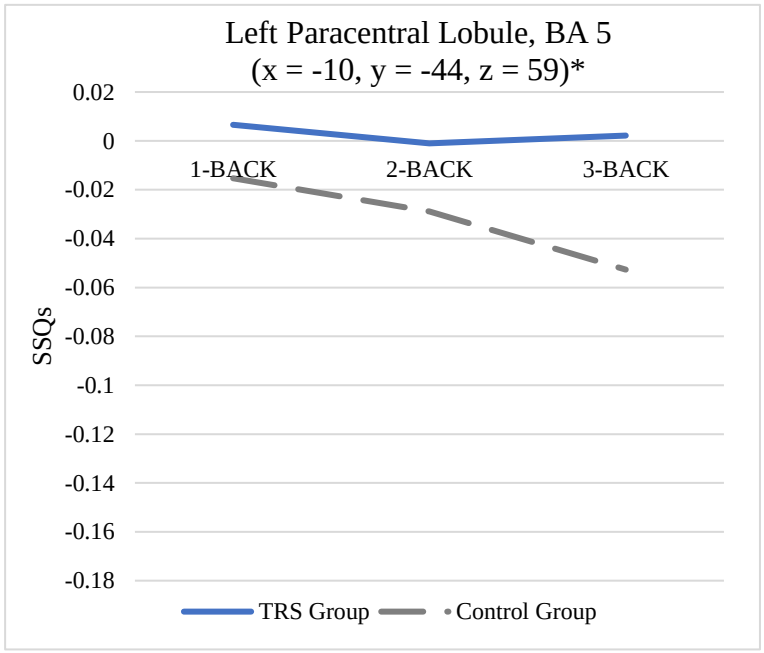
	1-Back	2-Back	3-Back
Control Group	0.01987	0.06328	0.04884
TRS Group	-0.01670	-0.00130	-0.00229
* Significant at p = 0.01211			

	1-Back	2-Back	3-Back
Control Group	0.03630	0.04798	0.06790
TRS Group	0.00162	0.01399	0.01214
* Significant at p = 0.01237			

	1-Back	2-Back	3-Back
Control Group	-0.00517	0.02927	0.00608
TRS Group	-0.00323	-0.01543	-0.02303
* Significant at p = 0.01404			

Figure 3. 26 Haemodynamic response as cognitive load increased in TRS participants and controls in the left Cingulate Gyrus (BA 31) and left Paracentral Lobule (BA 5).



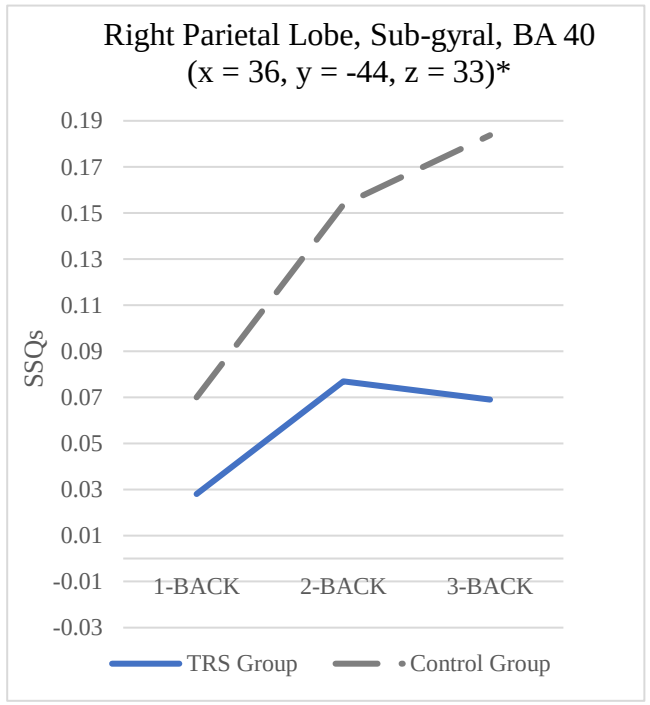


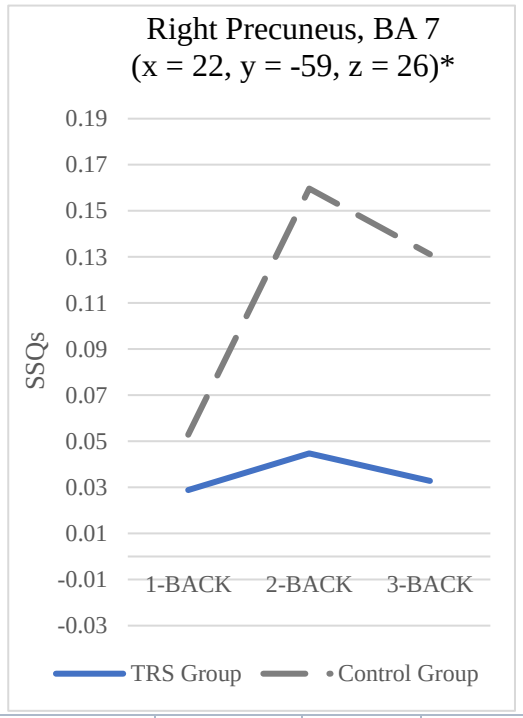
	1-Back	2-Back	3-Back
TRS Group	-0.02445	-0.07498	-0.04491
Control Group	-0.04412	-0.11562	-0.16391
* Significant at p = 0.00448			

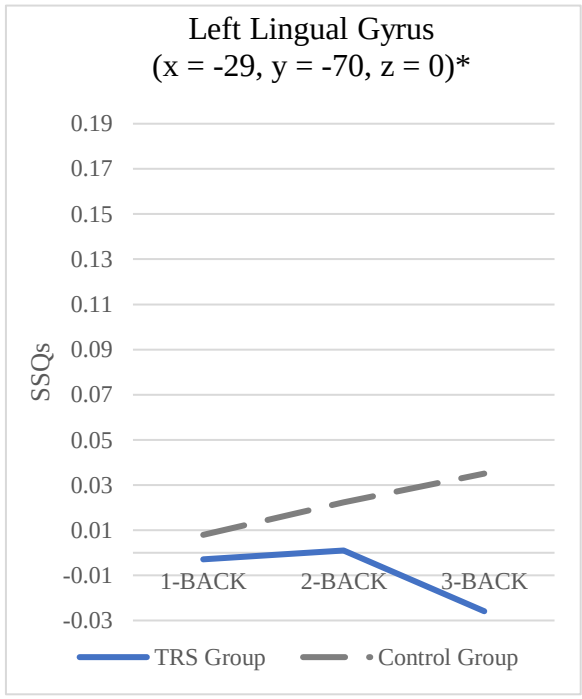
	1-Back	2-Back	3-Back
TRS Group	0.00659	-0.00102	0.00218
Control Group	-0.01530	-0.02891	-0.05269
* Significant at p = 0.01385			

¬ Nearest grey matter 6.9mm from first set of co-ordinates at -7, 30, 33, so alternative set given by XBAM used.

Figure 3. 27 Haemodynamic response as cognitive load increased in TRS participants and Controls in the right Parietal Lobe, sub-gyral (BA 40), right Precuneus (BA 7) and left Lingual Gyrus.







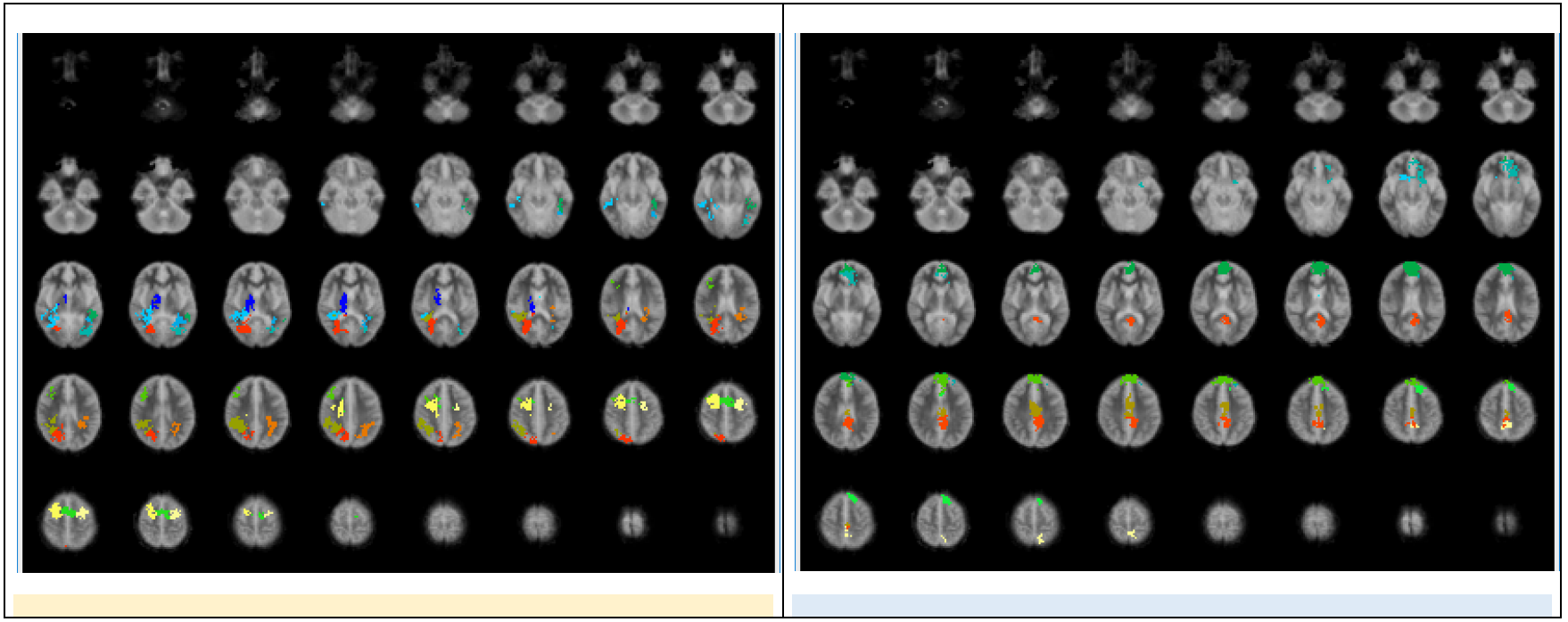
	1-Back	2-Back	3-Back
Control Group	0.06997	0.15356	0.18375
TRS Group	0.02800	0.07691	0.06899
* Significant at p = 0.00505			

	1-Back	2-Back	3-Back
Control Group	0.05284	0.15967	0.13115
TRS Group	0.02883	0.04474	0.03282
* Significant at p = 0.00721			

	1-Back	2-Back	3-Back
Control Group	0.00794	0.02230	0.03506
TRS Group	-0.00297	0.00100	-0.02589
* Significant at p = 0.01211			

- *Statistical Maps*

Figure 3. 28 Statistical Maps of the Factorial Interaction between TRS Participants and Controls

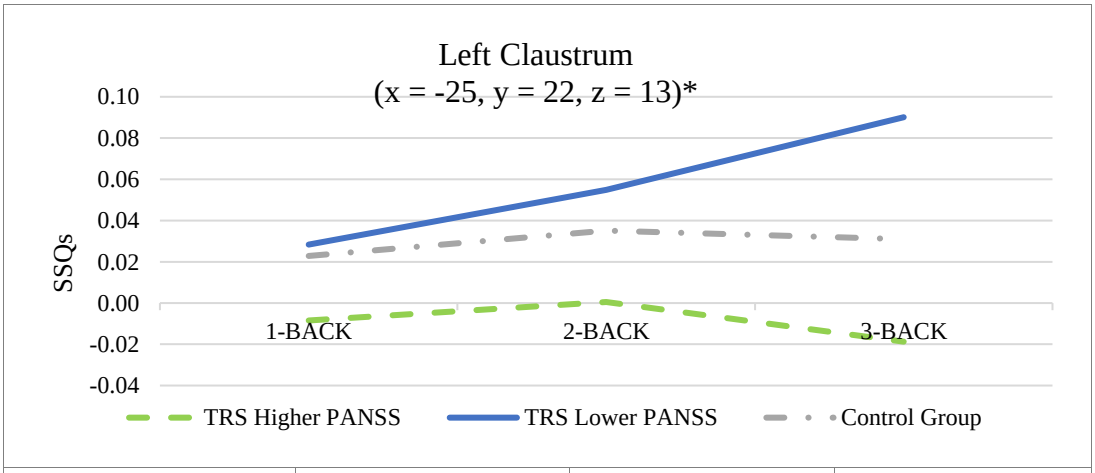


3.11 Factorial Analysis Comparing TRS Individuals Grouped by Symptom Severity (Lower vs. Higher PANSS)

Table 3. 25 Differences in the haemodynamic response between with higher and lower symptom groups (Lower versus Higher PANSS)

Anatomical Location	Brodmann Area	Hemis-phere	Cluster size (mm^3)	p-Value	Talairach co-ordinates* x	y	z
Superior Frontal Gyrus,	BA 9	L	57	0.00753	-7	56	26
Medial Frontal Gyrus	BA 9	R	50	0.00966	7	48	26
Middle Frontal Gyrus	BA 9	L	76	0.00279	-36	26	30
Claustrum	-	L	111	0.00542	-25	22	13
Inferior Frontal Gyrus	BA 9	L	100	0.00669	-43	4	23
Postcentral Gyrus	BA 3	R	482	0.00587	43	-19	43
Supramarginal Gyrus	BA 40	L	89	0.00303	-41	-46	33

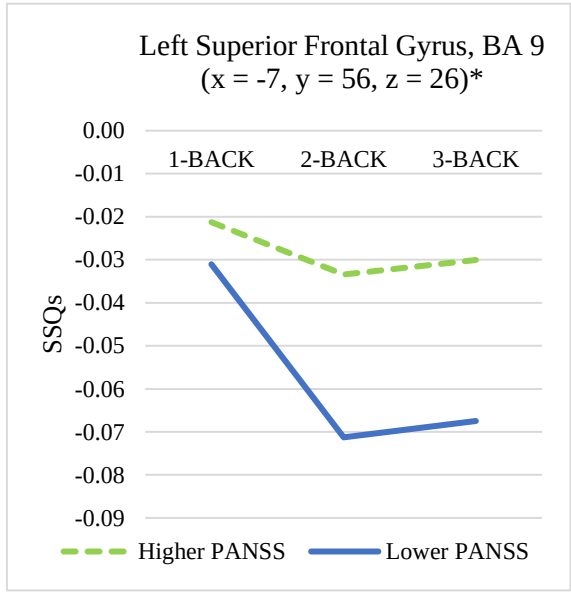
Figure 3. 29 Haemodynamic response in the left Claustrum at different levels of cognitive load in TRS individuals grouped by symptom severity.



	1-Back	2-Back	3-Back
Higher PANSS	-0.008391	0.000504	-0.018727
Lower PANSS	0.028348	0.054817	0.090098
Control Group	0.022842	0.035109	0.031020

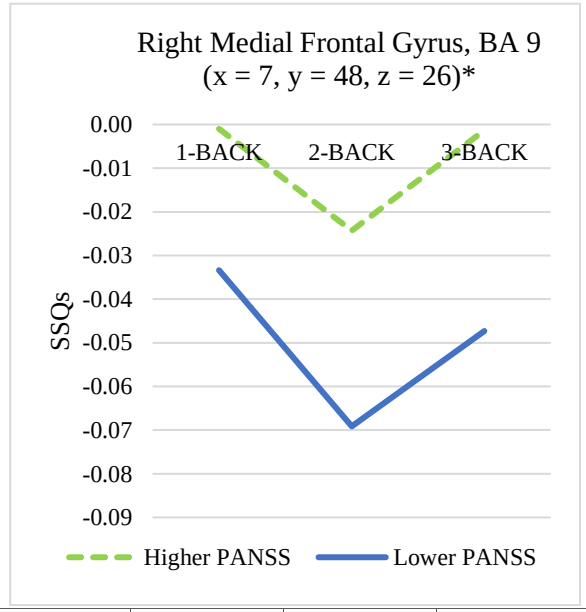
* Significant between Higher and Lower PANSS Groups at p = 0.00542
Note: Activation in the control group is shown for comparison. The difference with the TRS group as a whole was not significant in the main factorial analysis.

Figure 3. 30 Haemodynamic response in the left Superior Frontal Gyrus (BA 9), right Medial Frontal Gyrus (BA 9) and the right Postcentral Gyrus (BA3) at different levels of cognitive load in TRS individuals grouped by symptom severity.



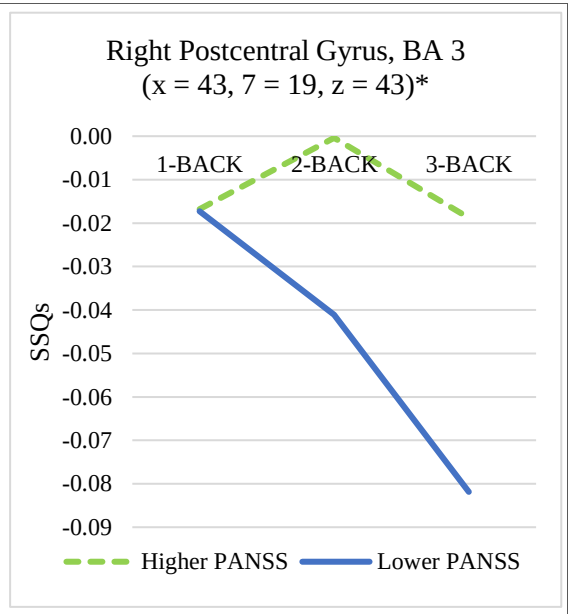
	1-Back	2-Back	3-Back
Higher PANSS	-0.02126	-0.03342	-0.03002
Lower PANSS	-0.03105	-0.07128	-0.06750

* Significant at p 0.00753



	1-Back	2-Back	3-Back
Higher PANSS	-0.00099	-0.02431	-0.00135
Lower PANSS	-0.03337	-0.06913	-0.04733

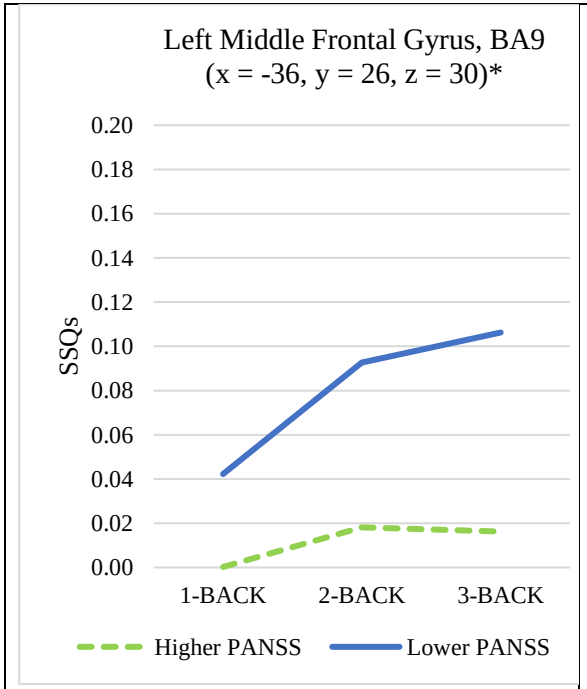
* Significant at p = 0.00966



	1-Back	2-Back	3-Back
Higher PANSS	-0.01677	-0.00038	-0.01879
Lower PANSS	-0.01728	-0.04107	-0.08186

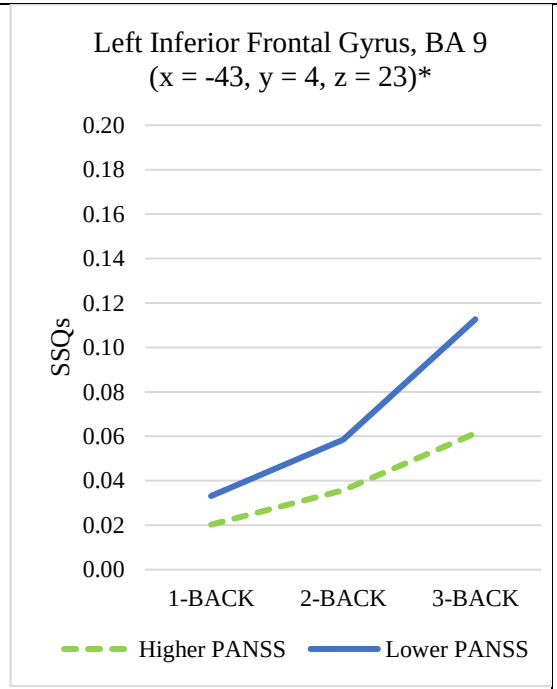
* Significant at p = 0.00587

Figure 3. 31 Haemodynamic response in the left Superior Frontal Gyrus (BA 9), right Medial Frontal Gyrus (BA 9) and the right Postcentral Gyrus (BA3) at different levels of cognitive load in TRS individuals grouped by symptom severity



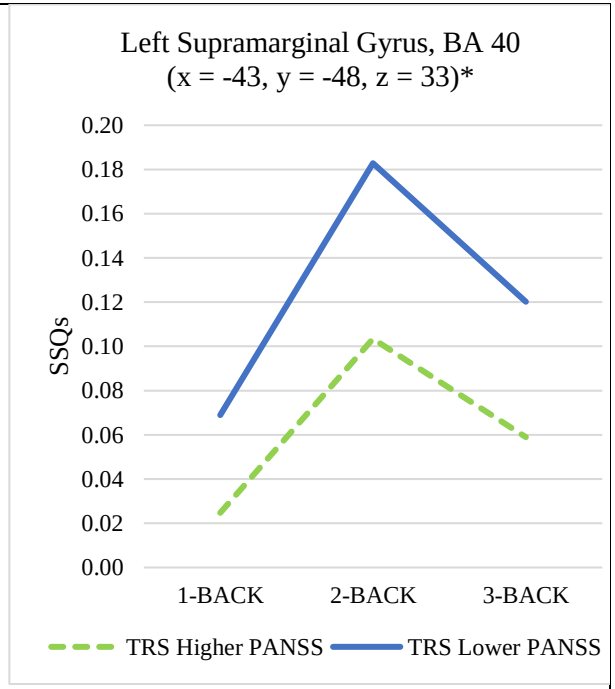
	1-Back	2-Back	3-Back
Higher PANSS	0.00023	0.01815	0.01627
Lower PANSS	0.04226	0.09275	0.10627

* Significant at p = 0.00279



	1-Back	2-Back	3-Back
Higher PANSS	0.02025	0.03571	0.06136
Lower PANSS	0.03313	0.05850	0.11267

* Significant at p = 0.00669

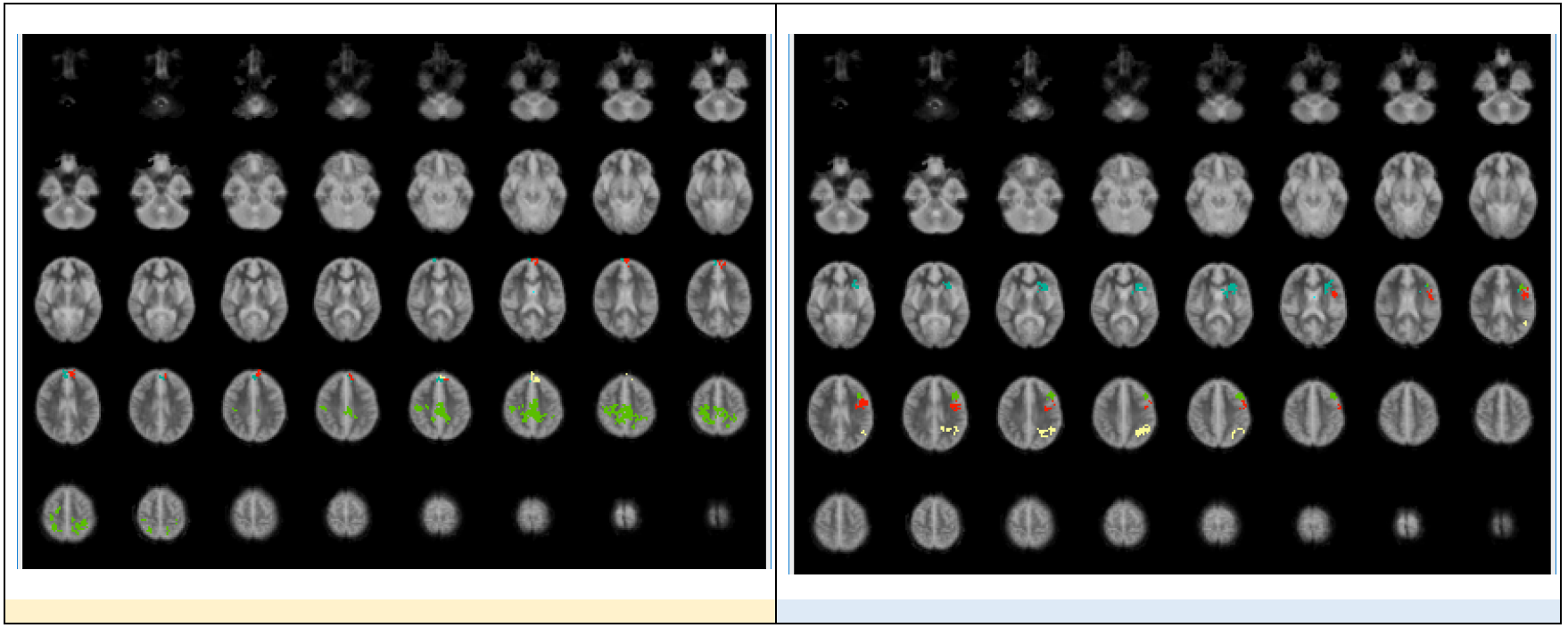


	1-Back	2-Back	3-Back
Higher PANSS	0.02474	0.10343	0.05899
Lower PANSS	0.06894	0.18283	0.12024

* Significant at p = 0.00303

- *Statistical Maps*

Figure 3. 32 Statistical Maps of the Factorial Interaction between TRS Participants Grouped According to Symptom Severity (Lower and Higher PANSS) and Cognitive Load



3.12 Correlational Analyses of the Haemodynamic Response at different levels of Cognitive Load and Symptom Severity in the TRS Group

The following analyses were conducted in XBAM (using the correlational option, BBAM) to explore relationships between the haemodynamic response and positive and negative symptoms in TRS group.

3.12.1 With Positive Symptoms

- *positive correlations*

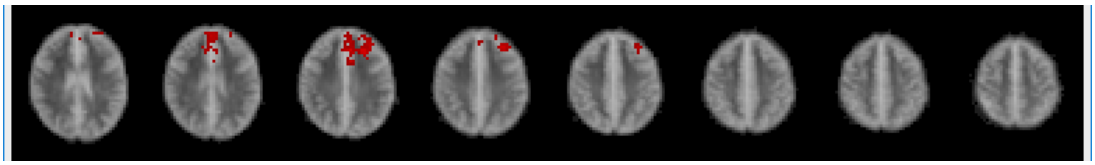
Table 3. 26 Brain areas showing significant positive correlation between positive symptom scores and the haemodynamic response in the TRS group

Anatomical Location	Brodmann Area	Hemis-phere	Cluster size (mm^3)	p-Value	Talairach co-ordinates* x	y	z
1-BACK							
Left Medial Frontal Gyrus	BA 6	L	119	0.00217	-18	30	33
2-BACK							
Non-significant.							
3-BACK							
Non-significant.							

Voxel-wise p-value = <0.05, cluster-wise p= 0.01.
Note: Age and reaction times in the baseline condition of the n-back task were covariates.

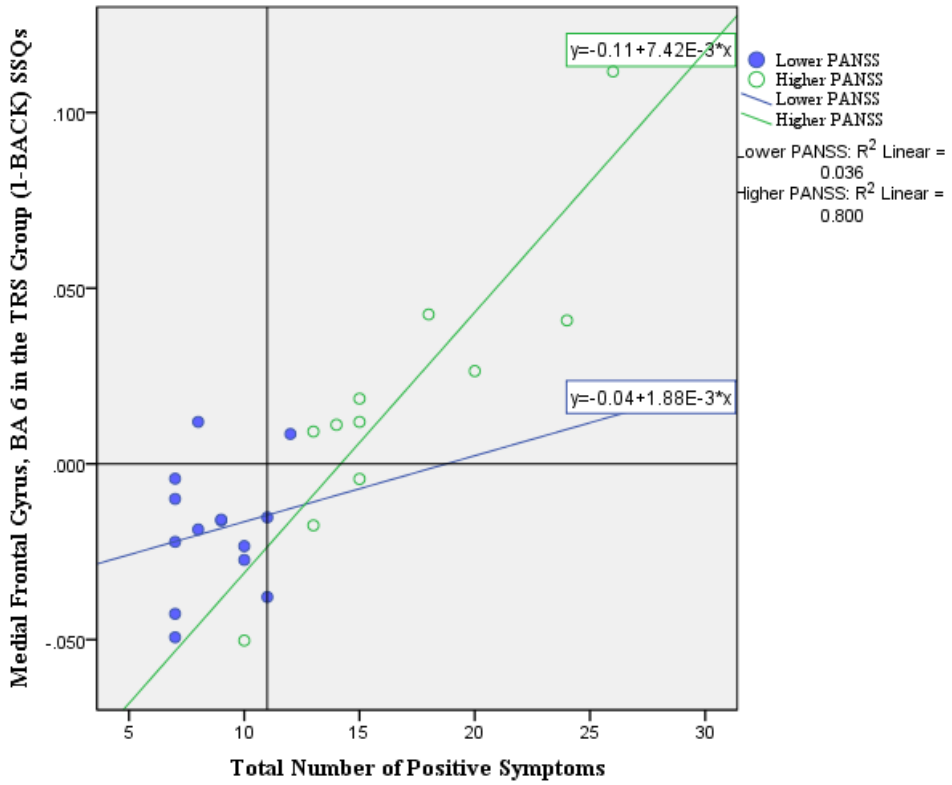
Figure 3. 33 Statistical Map showing a significant positive correlation between positive symptoms scores and the haemodynamic response in the left Medial Frontal Gyrus (BA6) during the 1-Back condition in the TRS Group

1-BACK



Positive correlation between the level of positive symptoms and the haemodynamic response in the Medial Frontal Gyrus (BA 6).

Figure 3. 34 Positive correlation between positive symptom scores and the haemodynamic response in the left Medial Frontal Gyrus (BA 6) during the 1-Back condition in the TRS Group



Notes: Vertical line indicates the median number of positive symptoms at 11.
Lines of best fit shown for lower and higher PANSS subgroups, n = 14, n = 11.

There were no significant negative correlations between the haemodynamic response and positive symptoms at any level of cognitive load with both age and mean RTs in the 0-Back condition as covariates.

3.12.2 With Negative Symptoms

- positive correlations

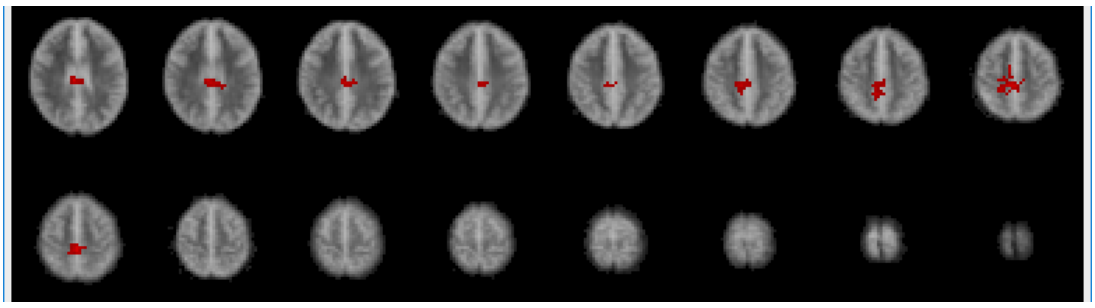
Table 3. 27 Brain areas showing significant positive correlation between negative symptoms and the haemodynamic response at different levels of cognitive load in the TRS Group

Anatomical Location	Brodmann Area	Hemis-phere	Cluster size (mm^3)	p-Value	Talairach co-ordinates* x	y	z
1-BACK							
Non-significant							
2-BACK							
Medial Frontal Gyrus	BA 6	R	155	0.00256	4	-26	53
3-BACK							
Postcentral Gyrus	BA 40	L	210	0.00239	-33	-37	50

Voxel-wise p-value = <0.05, cluster-wise p= 0.01.
Note: Age and reaction times in the baseline condition of the n-back task were covariates.

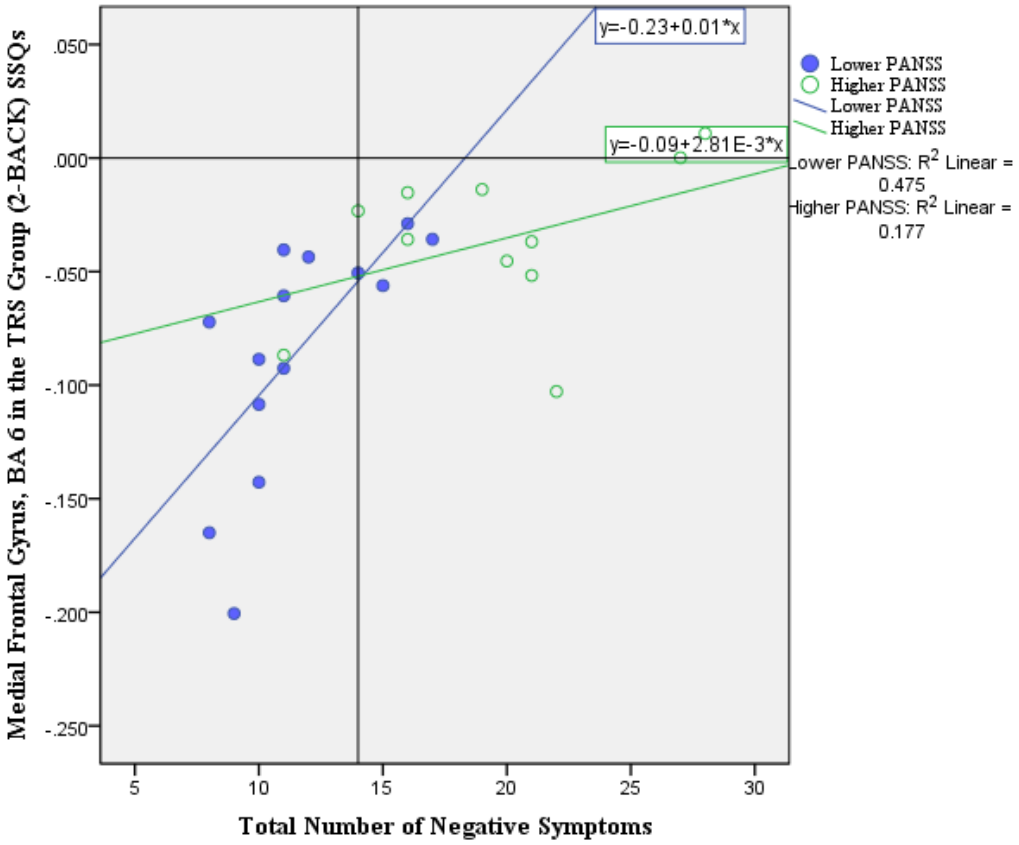
Figure 3. 35 Statistical Map showing a significant positive correlation between negative symptom scores and the haemodynamic response in the right Medial Frontal Gyrus (BA 6) during the 2-Back condition in the TRS Group

2-BACK



Positive correlation between the level of negative symptoms and haemodynamic response in the medial frontal gyrus (BA 6). (Note: the precuneus is prominent in this cluster although it was not labelled as a peak activation in XBAM).

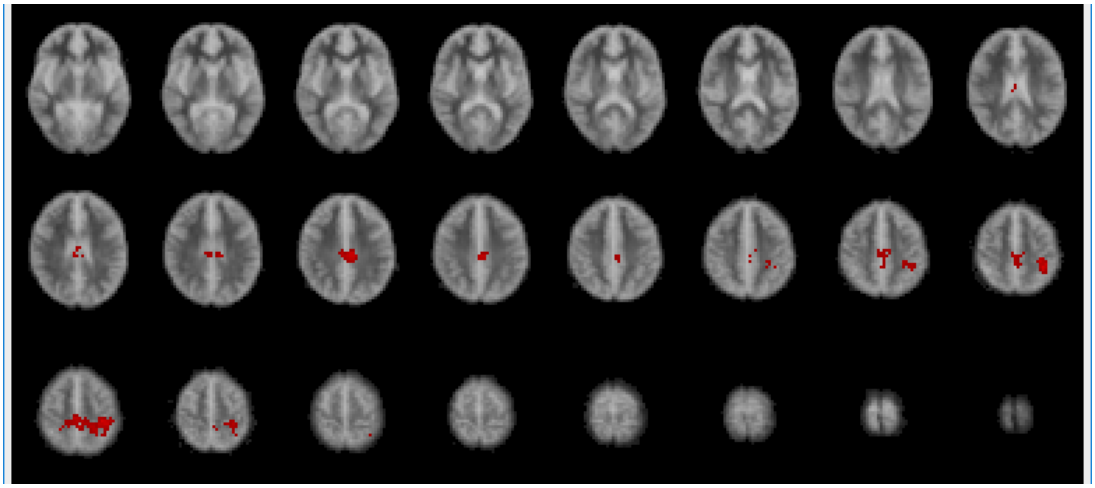
Figure 3. 36 Correlation between negative symptom scores and the haemodynamic response in the right Medial Frontal Gyrus (BA 6) during the 2-Back condition in the TRS Group



Notes: Vertical line indicates the median number of negative symptoms at 14.
Lines of best fit shown for lower and higher PANSS subgroups, n = 14, n = 11.

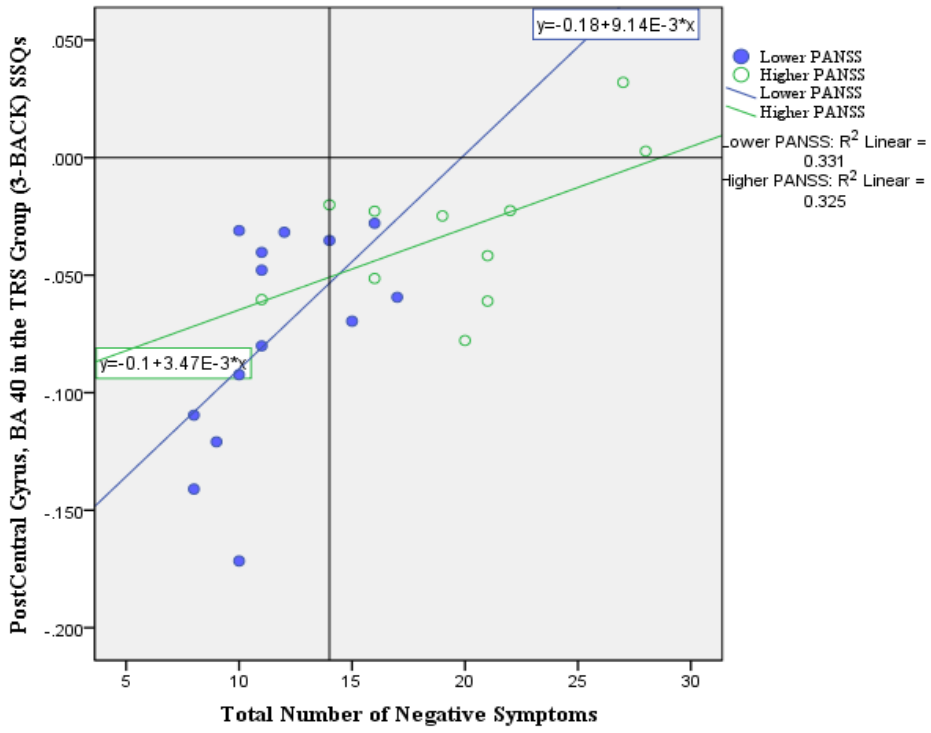
Figure 3. 37 Statistical Map showing a significant positive correlation between negative symptom scores and the haemodynamic response in the left Postcentral Gyrus during the 3-Back condition in the TRS Group

3-BACK



Positive correlation between negative symptoms and the haemodynamic response in the left Postcentral Gyrus.

Figure 3. 38 Correlation between negative symptom scores and the haemodynamic response in the left Postcentral Gyrus (BA 40) during the 3-Back condition in the TRS Group



Notes: Vertical line indicates the median number of negative symptoms at 14.
Lines of best fit shown for lower and higher PANSS subgroups, n = 14, n = 11

- *negative correlations*

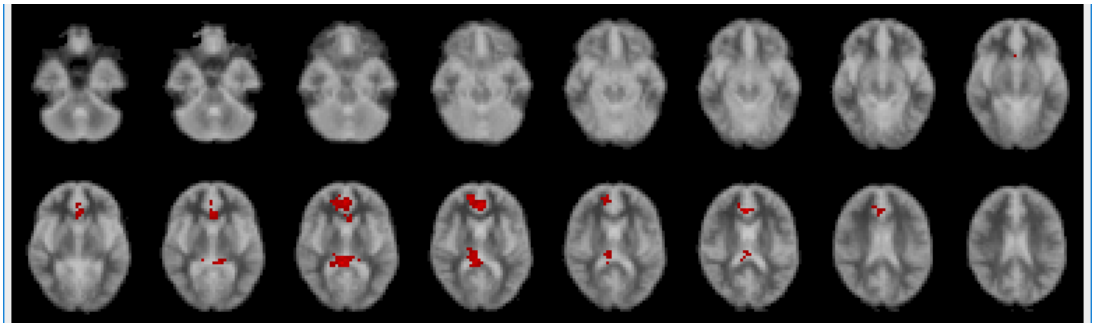
Table 3. 28 Brain areas showing significant negative correlation between negative symptom scores and the haemodynamic response at different levels of cognitive load in the TRS Group

Anatomical Location	Brodmann Area	Hemis -phere	Cluster size (mm^3)	p-Value	Talairach co-ordinates* x	y	z
1-BACK							
Non-significant.							
2-BACK							
Non-significant.							
3-BACK							
Anterior Cingulate Cortex	24	R	107	0.00259	4	33	17
Parahippocampal Gyrus (Nearest gray 5.4mm away)	30	R	74	0.00377	11	-40	5

Voxel-wise p-value = <0.05, cluster-wise p= 0.01.
Note: Age and reaction times in the baseline condition of the n-back task were covariates.

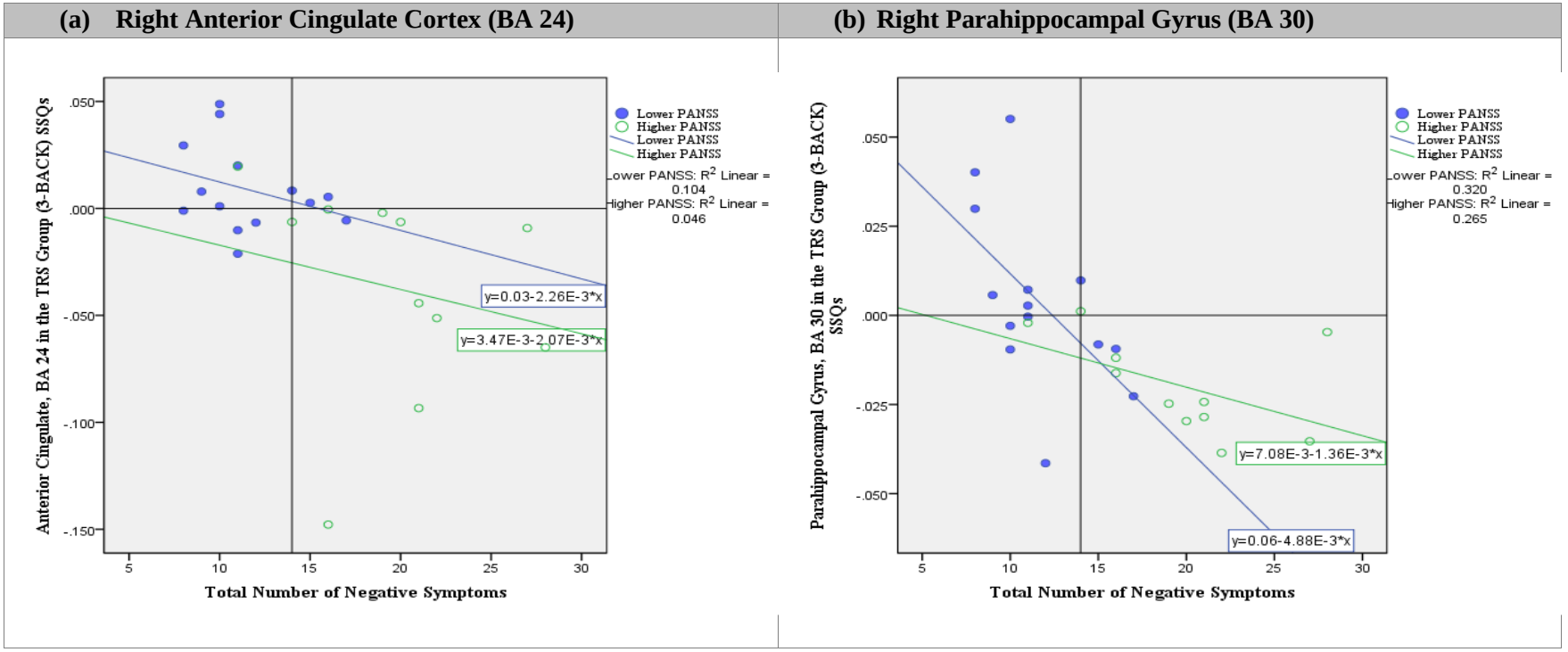
Figure 3. 39 Statistical Map showing significant negative correlation between negative symptom scores and the haemodynamic response in the right Anterior Cingulate Cortex (BA 24) and right Parahippocampal Gyrus (BA 30) during the 3-Back condition in the TRS Group

3-BACK



Negative correlation between negative symptoms and the right Anterior Cingulate Cortex and the right Parahippocampal Gyrus.

Figure 3. 40 Negative correlations between negative symptom scores and the haemodynamic response and in the right Anterior Cingulate Cortex (BA 24) and right Parahippocampal Gyrus (BA 30) during the 3-Back condition in the TRS group



Notes: Vertical line shows median for negative symptoms at 14. Lines of best fit shown for lower and higher PANSS subgroups, n = 14, n = 11.

CHAPTER IV - DISCUSSION

4.1 Overview and Organisation of the Discussion

TRS is a category which is currently not recognised by the main psychiatric classification systems, which has suffered from the lack of a consistent definition in the literature and has been relatively under-researched. Therefore, the nature of this study is inevitably largely exploratory. Moreover, this enquiry is set within the over-arching question as to whether TRS might represent a distinctive aetiopathological subgroup of schizophrenia, or is simply a more severe form of the disorder? The epidemiological evidence of Wimberley et al. (2016), which observed a lack of sex difference in TRS, along with an earlier age of onset, together with observations of normal presynaptic dopamine capacity in the associative striatum (Demjaha et al., 2012; Kim et al., 2017) provide a biological basis for a distinctive subtype. Nonetheless, the question cannot be settled without further evidence since understanding schizophrenia more generally remains one of the great challenges of neuroscience, but it is in the background prompting and guiding, nonetheless.

The main hypothesis of the current body of work was that TRS participants would, during the performance of a verbal n-back task, show attenuated engagement of an "executive" fronto-parietal network similar to that described for healthy controls in an earlier meta-analysis of n-back fMRI studies by Owen et al. (2005), and meta-analyses of studies comparing individuals with schizophrenia and healthy controls (Glahn et al., 2005; Minzenberg et al., 2009).

None of these studies specifically addressed TRS. The results of this thesis supported this hypothesis as the groups with the higher level of pathology (TRS participants relative to controls) displayed attenuated haemodynamic responses with increasing cognitive load in the frontal and parahippocampal gyri bilaterally, the right thalamus, right parietal lobe, right precuneus and left lingual gyrus compared to the control group. They also showed increased haemodynamic response in the right putamen, left medial/superior frontal gyri, left cingulate gyrus and left paracentral lobule.

Similarly, the higher PANSS group exhibited an attenuated haemodynamic response with increasing cognitive load in the left claustrum and left frontal gyrus, relative to the lower

PANSS group, as well as increased haemodynamic response in left superior frontal, right medial frontal and right postcentral gyri.

The behavioural and neuropsychological analyses in the TRS group revealed estimated IQ scores clustered around the peak of the normal distribution yet scores on the MCCB domains were consistently depressed relative to standardisation norms for the general population. Also, scores were superior in the lower PANSS group on the speed of processing composite, the test of visual learning, and for attention and vigilance, all at trend level significance. Further, exploratory correlations revealed negative symptoms were strongly associated with decrements in attention and also with estimated full-scale IQ and verbal IQ scores. However, the presence of intellectual asymmetries between the WASI subscales in 52% of TRS participants, with two polarised groups, complicates interpretation.

The results of this thesis contribute to the search for further biomarkers to distinguish TRS from FLRS. These results suggest the involvement of a common circuitry which has a rostral focus in the striatal-thalamocortical loops and ACC (see Weinstein et al., 2017 in relation to dopamine pathways), including the motor cortex and DLPFC, extending to the parietal and temporal association cortices. Important to efficient function, the large-scale networks of the salience network and DMN are implicated as well. However, the primary pathology may start in different areas in TRS and FLRS, but with the progression of pathophysiological processes they may increasingly resemble each other, for example, exhibiting deficits in GABAergic interneurons and GAD enzymes, grey and white matter abnormalities along with behaviours and clinical symptoms. Also, dopaminergic and glutamatergic neurotransmitter systems interact, for example, where receptors are present on the same neuron. It follows that the most distinctive biomarkers for both TRS and FLRS may be present early on in the disease and might also be found in unaffected first-degree relatives.

Further, in the light of evidence in this study that verbal and visual learning may deteriorate during episodes of acute psychosis before a trial of clozapine is tried, it is proposed that metabolically overactive brain areas (possibly consequent upon decrements in GABAergic inhibition), might become underactive as chronicity progresses, perhaps through degenerative changes or deficits in neural transmission and synaptic plasticity. Further, as proposed in section 1.7.3, ultra-TRS might reflect a more advanced form of TRS with possible support in the lower perfusion values of non-responders to clozapine in the SPECT studies of Rodriguez et al. (1997; 1998) where there might be a relative loss of function from which recovery is more difficult. By contrast, the therapeutic response to clozapine

appears to have involved reductions in perfusion values irrespective of whether an area was hyperactive or relatively hypoactive in relation to the values in a normative database (in the thalamus, basal ganglia bilaterally, superior DLPFC and anterior PFC bilaterally). The only region of interest where treatment with clozapine did not significantly lower perfusion values in responders was in the inferior DLPFC bilaterally). A significant decrease in the anterior prefrontal area in responders may also be consistent with hyperactivity in the ACC in some TRS individuals, at least, before clozapine treatment is initiated (Demjaha et al., 2014; Mouchlianitis et al., 2016 (a). Of course, other explanations could apply to ultra-TRS, not least a history of chronicity and different treatments, also, a loss of function might be predicted to be associated with greater atrophy in related areas.

This discussion will start with the clinical, neuropsychological and behavioural aspects, followed by the main results of the neuroimaging study which are to be found in the factorial analyses, along with a brief discussion of some of the "hub" areas and networks that are implicated in this study. This is intended to provide further perspective on the results of the trend analyses and correlations between the haemodynamic response and behaviour which follow. The main findings will be summarised in a model which characterises TRS along with pertinent observations in the wider literature (section 5.1). Some limitations will then be highlighted, followed by some ideas for further research.

4.2 Clinical, Neuropsychological and Behavioural aspects

4.2.1 Participant characteristics

- A low level of symptoms

In view of their TRS status, it was striking that many participants presented with low levels of clinical symptoms, indeed the median total PANSS scores for the group as a whole was only 45 (min-max: 37-90, n=26), on a measure where the minimum score is 30 (one point is given for an absence of pathology) and the maximum possible PANSS score is 210, but may be rarely achieved. A better reference point might be found in studies of chronically unwell individuals, partially or wholly refractory to treatment, for example, in Zink et al., (2009) at 84 (SD=11.2) or Honer et al., (2006) at 102.5 (SD=15.8). A 20% reduction in symptoms defines the clinical response for in some drug trials (e.g. Cipriani et al., 2009), while a 50% reduction in these studies (yielding 42 and 51) would be closer to scores in this study.

The low scores are surely indicative of the efficacy of clozapine however, they might also be a function of participant selection. While it is often the case that participants may not be representative of their peers, it is wondered if this might be particularly true of the clinical participants in this study as recruitment proved very difficult. Several people, to whom I am indebted, became involved, often making fruitless visits to clinics. Samanaite et al., (2018) commented "patients who are about to start clozapine can be difficult to recruit to research involving neuroimaging or invasive procedures because they are often very unwell and may lack capacity to consent." (p.24) However, in the light of the experience here, perhaps, the persistence of some negative or cognitive symptoms undermine motivation despite an overall reduction in symptom scores? Fatigue might be a further or exacerbating reason as clozapine can have sedative effects (Thompson et al., 2014).[51] Sometimes an individual may be reluctant to participate if they feel they have been let down as patients.[52]

4.2.3 Cessation of Smoking – a sign of clinical improvement?

A high prevalence of smoking has often been observed in schizophrenia and 92% of the TRS group indicated they had been nicotine dependent at some point. However, there was a reduction in the lower PANSS group compared with the higher PANSS group, even though smoking was still highly prevalent in the lower PANSS group at 65.3%. The lower PANSS group had been attending clozapine clinics for a longer period and there is considerable incentive to reduce smoking because this may permit the lowering of the clozapine dose due to metabolic factors, therefore, the lower PANSS group had a longer time to respond to this message. However, this could be over-stated since the median period of clozapine treatment was 4.5 years in the higher PANSS group. An alternative possibility is that some individuals in the lower PANSS group felt well enough to stop smoking .

There is evidence on both sides of the "self-medication" hypothesis, e.g. Boggs et al. (2017) recently disputed it (although it may be relevant their participants had few negative symptoms and only one was taking clozapine, so perhaps they did not have deficits which could be further relieved by nicotine). However, substantive evidence points to nicotine having neuromodulatory effects with amelioration of negative symptoms. Smucny et al., (2017) observed hypoconnectivity between the ACC and ventrolateral PFC during a placebo (no nicotine) condition in their PSZ group relative to healthy controls; also,

[51] One participant told me about their "bad days" when they just sit all day.

[52] One person approached me to say they wouldn't be taking part in the study but wanted to say they were angry that trial of clozapine hadn't been tried earlier.

hyperconnectivity between nodes of the salience network (the insula and middle cingulate cortex). The latter also correlated with the severity of negative symptoms (anhedonia and asociality) during the placebo condition when nicotine was not administered to individuals with schizophrenia (all participants had not smoked for a minimum of 3 months). It was further observed nicotine affected connectivity between the ACC and the CEN and also "betweenness centrality" in the ACC where the high betweenness centrality of the salience network may help it "to integrate information and process salience." (p.86) Similarly, Smucny et al. (2017) have observed:

The hypothesized role of the salience network in switching between task-positive and task-negative network dominant states as a function of cognitive demands (Menon, 2011; Palaniyappan and Liddle, 2012) suggests that nicotine may improve cognition in schizophrenia (Barr et al., 2008; Harris et al., 2004) via its ability to increase the integrative capacity of the network. (p.94)

In their study, short term abstinence increased omission errors to targets on a CPT task for both PSZ and controls who smoked and it was suggested this may have been mediated by tobacco cravings, however, spatial working memory performance was impaired only in the schizophrenia group and improved upon resumption of smoking.

It was also interesting that Smucny et al. (2017) chose to highlight the role of von Economo neurons (VENs):

The ability of nicotine to affect betweenness centrality of the ACC may be related to the presence of specialized neurons in the area called von Economo or "spindle" neurons. Von Economo neurons are unusually long (160-200 mm or more) neurons that are exclusively present in the ACC and insular cortices..... The unique morphology of these cells is thought to enable these brain areas to communicate with distal sites, facilitating their ability to integrate information from many sources to aid in complex computations associated with high-level cognitive functions, e.g. social behavior (Butti et al., 2013). (p.94)

Decrements in VENs had been observed in early onset schizophrenia (Brune et al., 2010) and their presence has now been established in the ACC, Insula and DLPFC in humans and if TRS is characterised by impairments in global connectivity then this could be an important area of enquiry (also see: Allman et al., 2010, 2011; Nimchinksy et al., 1995, 1999; Hakeem et al., 2009; Stevens et al., 2011). Certainly, rapid and accurate assessment of social situations would have survival value and it is noted that the social cognition had

the lowest scores on any individual test, just below the 3rd percentile for both lower and higher PANSS groups.

Interestingly, smoking status was observed to affect emotional recognition scores in the study comparing cognitive profiles in TRS, FLRS, U-TRS and healthy controls in the study by Anderson et al. (2015,b) to the extent it was entered as a covariate in their analyses. Performance on this task also correlated with negative symptoms in their FLRS group and both with verbal memory and verbal fluency in their TRS group. However, the task which involved judgements based on faces had fewer individuals exhibiting deficits than the FLRS or U-TRS groups and appeared more similar to the controls. While, in this study scores may have been affected by some unfamiliar American vocabulary (e.g. "tractor-trailer truck"). Also, the reading skills of the group were not tested and a printed sheet of the scenarios being described may have been unhelpful to some participants.

4.2.4 Other Substance Use

Table 3. 4 indicated there were no significant differences between the higher and lower PANSS groups on the prevalence of drug use prior to the first episode of psychosis. While doubt should be cast on the accuracy of recall concerning distant events, a high prevalence of drug use is not unusual in schizophrenia populations although it may be under-reported (Bahorik et al., 2014, a; Bahorik et al., 2014, b), so it would be unsurprising if drugs were also taken in the prodrome (among the participants this would have been approximately between 1985 and 2003). A link between psychosis and cannabis which has dopaminergic effects has been established (Marconi et al., 2016), although earlier types of cannabis may have been less potent. Also, the use of ecstasy which has serotonergic, dopaminergic and cholinergic actions (Annenken et al., 2013) may have been less common than today. However, the use of LSD reported by 40% of the group was particularly concerning and, apparently, is becoming fashionable again (Pollan 2018).

4.2.5 Time to Access Clozapine

Recent statistics for England and Wales, indicate 23.7% of individuals with schizophrenia are receiving clozapine but it could not be ascertained why a trial of clozapine had not been tried in some individuals with TRS (Patel et al., 2014). In this study, the median average time to access clozapine in the higher PANSS group was 7 years and the median delay in the lower PANSS group was 4-years (Table 3. 3). The latter is like Taylor et al. (2003), whose study of antipsychotic prescribing in the South London and Maudsley NHS

Foundation Trust in a temporally overlapping cohort, observed a mean delay of nearly 4 years in individuals who commenced clozapine between 1.1.2006 and 15.4.2010. National Institute of Clinical Excellence guidelines recommend a trial of clozapine should be initiated as soon as possible for TRS (Howes et al., 2012; Taylor, et al., 2003).

Among those in the higher PANSS group, were three individuals who had only started clozapine in the previous year. In a further case, there had been earlier concerns about adherence, so the duration of treatment may have been an over-estimate. As clozapine can take 6-12 months before the benefit is more fully apparent (Lieberman et al., 1994; Fabrazzo et al., 2002), shorter treatment duration might help to explain a higher level of symptoms. Estimates indicate the higher PANSS group had received clozapine for around half the period of the lower PANSS ($p = 0.016$) so delays in accessing clozapine and a shorter duration of treatment might contribute to greater pathology.

Earlier studies on the duration of untreated psychosis in the prodrome have been mixed in PSZ. However, relapse in the first year appears to be a predictor of cognitive outcomes (Rund et al., 2016), which could be pertinent to TRS. Exploratory correlations were conducted on access and duration of treatment with clozapine and are reported in section 3.1.2 (and Table Appx. 4. 7 where they were mostly non-significant). However, it is interesting to note those who had waited the shortest time before their first trial of clozapine were among the more recently diagnosed, which is consistent with the prescribing guidelines above being applied. There were no significant correlations with the duration of treatment with clozapine, however, if most benefit accrues within two years this sample cannot address this.

Relatively few of the selected correlations with the time to access to clozapine were significant, however, there was a highly significant (albeit unadjusted) negative correlation between the MCCB overall composite score and the time to access clozapine ($p = .007$, Table Appx. 4. 7, b). This is difficult to interpret since the overall composite score reflects many variables. Indeed, so does the WASI yet neither FIQ nor the subscales correlated with the elapse of time before clozapine, notwithstanding these were strongly and very significantly correlated with the overall composite score (Table 3. 9). Also, the overall composite scores were extremely low in this study, with a group median percentile of 2.3 (Table 3. 7), so it should be considered whether sufficient data informed the extremes of the distribution in the MCCB standardisation study: in a reply to Siu (2008), the authors (Kern et al., 2008) agreed that the values at the lower end of the distribution had been inferred

since “few subjects in the community normative sample scored at extremely low levels”, however, their sample met the assumptions of normality.

There was, however, a significant negative partial correlation where age at the time of the study was controlled, between the time to access a trial of clozapine and verbal learning (Figure 3. 5). Similarly, with free recall on the first trial of the HVLT-R (Table Appx 4. 7, b). There was also a significant negative partial correlation (again with age as a covariate) between the time to access a trial of clozapine and visual learning scores (Figure 3. 6). These significant partial correlations indicate that untreated acute psychosis may be neurotoxic with respect to processes associated with short term learning in both the visual and verbal domains. Possibly relevant to this, was the apparent lack of a recency effect during free recall on the first trial of the HVLT-R discussed in relation to the phonological short-term store below.

Further, the lack of correlation between the time to access clozapine variable with performance IQ might indicate fluid intelligence and the overlapping concepts of executive performance and working memory are less susceptible to illness progression during this period. However, the above observations could be consistent with the view that both verbal and visual learning could be affected by progressive deficits in synaptic plasticity (Friston et al., 2016; Stephan et al., 2009). A mediating factor might be the vulnerability of associated areas to glutamate excitotoxicity, which may be more likely to arise with acute psychosis. Similarly, this might help to explain the apparent lack of recency in free recall, although, alternative explanations are advanced (in Chapter 5). As previously discussed, vulnerability of myelin is one aspect; another is subunit composition at the NMDAR in the prefrontal cortex where the NR2B subunit may enhance learning but also increase the risk of damaging influxes of calcium ions (the “double-edged sword” described by Monaco et al., 2015).

4.2.6 Performance on the WASI

Estimated IQ in TRS participants was normal to good normal: median FIQ in the lower PANSS group at the 66th percentile was greater than the median score for the higher PANSS at the 39th percentile ($p = .04$ with a large effect size). Median statistics which minimise the effects of outliers also indicated PIQ scores across the entire TRS group were higher than VIQ scores (63rd percentile compared with the 47th; Figure 3. 1). This was also apparent in the depiction of differences between the subscales for individual participants (Figure 3. 2), which also revealed that for a minority (4 individuals) there was an asymmetry of 10 or more standard scores in the opposite direction where VIQ scores were higher than PIQ

(VIQ>PIQ grouping). In Figure 3. 3 which plots the level of negative symptoms against asymmetry between the scales, it was apparent that all the VIQ>PIQ individuals had very low levels of negative symptoms and so, as previously stated, might represent a confound in the data.

The evidence of intact intellectual performance on the WASI contrasts with a literature review by Ohi et al., 2017 (b) where 70% PSZ exhibited a marked decline of 30 points relative to premorbid IQ. However, higher WASI scores may be a function of participant recruitment rather being representative of TRS. Further, relatively high IQ may help to explain some excellent responses to clozapine: "High IQ can be a protective factor in that it is likely to be associated with better overall level of functioning and with better outcomes in schizophrenia" (Kremen et al., 2001 p.453).

4.2.7 Intellectual Asymmetry

Examination of the WASI subscales indicated around half the TRS group had an asymmetry. In 36% of TRS participants scores were higher on the PIQ whereas in 16% they were higher on the VIQ, while 48% exhibited less asymmetry, if at all. The verbal IQ subscales reflects crystallised intelligence or declarative knowledge such as vocabulary which can be extended through education and learning (including previous encounters with the WASI!), however, the performance subscale measure fluid intelligence is a relatively fixed attribute, so the relative superiority is harder to explain. Therefore, the observation of superior performance IQ in TRS individuals is intriguing and may be a rare observation. It was difficult to find reports of intellectual asymmetry in schizophrenia, however, they typically favour VIQ (Amminger et al., 2000).[53] Kremen et al. (2001), for example, using the Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler 1981), observed intellectual asymmetry favouring VIQ over PIQ in their sample of 36 PSZ which was present irrespective of whether IQ was in the low average (81-94) or average (95- 109) range, whereas performance between the subscales was more even in the control group.

In this study, a minimum difference of 10 points was considered to be meaningful in a distribution that clustered around the 50th percentile. This difference was also greater than those considered to be of clinical interest in a review of 12 studies on IQ asymmetry in brain injury by Hawkins et al., 2002, who observed VIQ is typically spared relative to PIQ in brain injury and the differences recede as individuals recover. Using the above criteria, 52%

[53] Kremen et al. (2001) citing Heaton and Drexler 1987: "higher verbal than performance IQ is the predominant pattern in schizophrenia," p.453.

of the sample in this study exhibited superior PIQ. By contrast, previous reports on intellectual asymmetry in schizophrenia have usually favoured verbal IQ over performance IQ. In Amminger et al. 2000, these were present premorbidly during adolescence (mean age 13.1 years, SD 3.2) and again at follow up about 18 years later (mean age 30.9, SD. 3.9).

However, the findings in this study could be a consequence of using the WASI to estimate IQ. Axelrod (2002) directly compared the accuracy of the WASI in estimating the FIQ and subscales of the WAIS-III with 72 clinical participants (66 had psychiatric or neurological diagnoses) and reported that WASI PIQ and FSIQ scores were higher than analogous WAIS-III scores, and that WASI VIQ was lower than WAIS-III VIQ (p.19). Such discrepancy bias may be important when interpreting the results of the current study, which showed higher PIQ compared to VIQ scores (the dominant asymmetry in Axelrod, 2002). It was concluded "the utility of estimating VIQ and PIQ with the WASI is difficult to endorse when less than one half of the clinical cases obtained scores within 6 points of their WAIS-III VIQ and PIQ scores." (p.22). This imbalance accords with the observations in this study where the 52% of the participants exhibited an asymmetry of 10 or more standard points.

Yet, the possibility of asymmetry raises some interesting questions. For example, whether this could reflect the incomplete lateralisation of language involving Broca's territory (in the vicinity of the inferior frontal gyrus) and Wernicke's territory (proximal to the superior temporal gyrus) which were reported (e.g. Bleich-Cohen et al. 2009; Chou et al., 2017). Neurological soft signs relating to motor function have also be attributed to atypical lateralisation (Niethammer et al. 2000), which might also be related to mistiming and related disruption to higher cognition, embodied in the concept of "cognitive dysmetria" (Andreasen et al., 1998; Varambally et al. 2006; Matsuo et al., 2013).

Recent advances in tractography have made it possible able to infer the strength of connections based on volumetric measures and found considerable variation in healthy populations. Taking the example of the long segment of the arcuate fasciculus[54] Catani et al. (2007), observed this had little or no presence in the right hemisphere in approximately 60% of right-handed healthy participants. While in the remaining 40%, this tract was bilaterally

[54] This perisylvian pathway runs medially, connecting the temporal and frontal cortex around the temporo-parietal junction. The pathway runs proximal to the inferior parietal cortex (angular gyrus BA39 and supramarginal gyrus, BA40), where parallel anterior and posterior segments ascend more laterally into the inferior parietal cortex of Geschwind's territory. In the dominant left hemisphere, the long segment connects Wernicke's territory (in the middle temporal gyrus posteriorly /temporo-parietal junction) and Broca's territory in the inferior precentral gyrus and posterior parts of the middle frontal gyrus; thereby implicating it in language function.

distributed with about half showing some leftward distribution. In addition, consistent with the view that hemispheric organisation increases with development, they commented that myelin organisation in this tract, as measured by fractional anisotropy, increases between the age 5 and 30 years. Variation in lateralisation has also been reported in sensory-motor pathways.

It is suggested here that PIQ tasks may typically involve activity that is more distributed across brain areas than VIQ ones, so efficient processing may involve greater reliance upon dynamic interactions with the default mode network and between the hemispheres involving major tracts such as the dorsomedial cingulum and parts of the corpus callosum. While representing a potential vulnerability as decrements in interhemispheric communication have been observed in schizophrenia (Hoptman et al., 2012), a more distributed system may be less vulnerable to local damage (for example, if it is possible for there to be local concentrations of excitoxocity). Also, there may also be greater opportunities for compensatory connections and mitigation through the redundancy available in rich club organisation, for example in bilateral hubs in the superior frontal and superiorparietal cortex, precuneus, putamen, thalamus and hippocampus identified by van den Heuvel and Sporns (2011); therefore, PIQ may be more spared from the consequences of "leftward pathology" which has been commented in studies of schizophrenia: for example, a systematic review of 46 studies by Sun et al. (2009) presented evidence of associations between the development of thought disorder and auditory hallucinations with volumetric reductions in the superior teral gyrus, particularly in the left hemisphere; also, a consortium study of 1985 individuals with schizophrenia reported in Walton et al. (2017) observed a significant association between negative symptoms and reductions in cortical grey matter and only in the left hemisphere. They further commented that atypical lateralisation in the schizophrenia literature may reflect "greater involvement of the right hemisphere, which may relate to a broader, more diffuse semantic network (Grabner et al., 2007)." p.8

The possibility of superior PIQ in some instances makes an opposite asymmetry reported by Kravariti et al. (2006) concerning 108 unaffected first-degree relatives all the more interesting. That study was consistent with earlier reports on intellectual asymmetry in schizophrenia which have usually favoured verbal IQ over performance, for example, Amminger et al. (2000) compared IQ premorbidly during adolescence (mean age 13.1 years, SD 3.2) and again at follow up about 18 years later (mean age 30.9, SD. 3.9) and observed relative decrements in PIQ preceded the onset of psychosis. Kravariti et al. (2006) proposed an intellectual VIQ>PIQ asymmetry might be endophenotype of schizophrenia.

4.2.8 A Comparison of scores on the MCCB relative to the WASI

The MCCB is relatively new and was designed to measure improvement in drug trials and there is still large a gap in the literature concerning how performance on the MCCB relates to IQ scores (August et al., 2012). However, it is a reasonable assumption that percentile scores on the MCCB may be predictive of scores on the WASI. Mohn et al. (2014) set out to address this and observed a high degree of correlation in their sample of 250 healthy participants. The strongest correlation was observed between FIQ and the composite score r =.60, which is also in agreement with this study: rho = .681, n=24, p = .001.

Mohn et al. (2014) further proposed that in the light of this some measures on the MCCB could be used to predict IQ, in order to reduce assessment times. All the domain scores, except for social cognition, correlated with FIQ. Certainly, in principle, this might be an efficient approach, for example, Ohi et al., 2017 have developed a WAIS-Short Form assessment involving a combination of "Similarities" from the verbal subscale of the WAIS-III and Symbol Search from the Performance subscale. However, in the case of the TRS participants in this study, further transformation of MCCB scores would be required as percentile scores on the MCCB were lower than those on the WASI. Also, there were some clear differences in correlations with the subscales (Table Appx. 4. 5), where neither symbol coding, spatial span nor NAB mazes scores correlated with VIQ. Moreover, social cognition did not correlate with PIQ scores and the speed of processing composite did not correlate with any of the WASI measures. The latter, being one of the four domains (along with working memory, visual and verbal learning) proposed by Mohn et al., (2014, p.100) that could be used to infer IQ level. However, this could be misleading in TRS if there is uneven deterioration with disease progression, as might be the case for visual and verbal learning. Also, some adjustment would be necessary as scores were depressed relative to the 50th percentile.

Nonetheless it is striking that MCCB scores in this study, unlike those in the WASI, were consistently below the 50th percentile, indeed, most were below the 16th percentile which approximates to 1 SD below the mean in a normal distribution. The best performance on an individual test was for the category fluency word generation task (animal names), which might suggest semantic organisation and processing post-encoding were relatively preserved. The worst score was for social cognition which approached 2SDs below the mean. In both tests, there was no difference in the median scores for the lower and higher PANSS subgroups. Indeed, there were no significant differences between these symptom groups for any of the tests (Table 3. 7).

Moreover, in direct comparison of FLRS, TRS and U-TRS, Anderson et al. (2015, b) concluded "treatment-resistant patients may not be more neurocognitively impaired than responders to first-line anti-psychotics and that patients with ultra-treatment-resistant schizophrenia perform similarly." (p.817) However, the mean age of their participants was in their early 30's so it seems likely that most had an established course of schizophrenia; also, TRS participants were on clozapine monotherapy which may have brought about some cognitive improvement so it is quite possible there had been a convergence in scores (as proposed in the preliminary comments to this discussion that different groups may increasingly resemble each other). It should also be noted that Anderson et al. (2015, b) did not use the MCCB, so their results are not necessarily equivalent, for example, their test of visual memory appears to have conflated visual learning and visual working memory.

Contrary to what may have been predicted on the basis of the wider schizophrenia literature, the performance on the working memory tests (letter-number span and spatial span at the 26th and 24th percentiles respectively) ranked only behind category fluency. This is in agreement with Lystad et al.'s (2014) study of 131 individuals with psychotic disorders (88.5% PSZ), who commented "A relatively unexpected result" of their Norwegian MCCB study of schizophrenia "was that working memory emerged as the least impaired domain in the patient group." (p.1098) It was also the case that working memory was far less impaired than verbal memory recall and recognition in Anderson et al. (2015, b).

Performance on the remaining tests drops towards and below the 10th percentile. (The next best performance for the TRS group as a whole, concerned the composite score of processing speed at the 10th percentile, although this was elevated by the inclusion of the category naming task as one of the 3 tasks). There was also a marked discrepancy in percentiles between the lower and higher PANSS groups for visual learning but this failed to reach significance. However, observation that scores in the lower PANSS group were generally higher was supported by the overall composite score (Table 3. 7) based on the ten tests which reached significance, $p = 0.024$, but would not survive Bonferroni correction. This score was markedly below the rest at 2.3 percentiles, which is also two standard-deviations below the mean. This is lower than might be expected on basis of the other scores, however, the designers of the MCCB acknowledge "a form of measurement bias can occur when comparisons are made with domains assessed by a single test" resulting from a renormalisation process that enables domain scores to have the same metric regardless of the number of tests:

The group difference in the domain score is adjusted by a factor that increases as a) the correlations between the component tests decrease and b) the number of tests increases. Intuitively, this is because when the correlations are imperfect, each test contributes additional unique variance in defining between group differences. (Kern et al., 2011, p.6)

4.2.9 A deficit in the phonological short-term store?

A Post Hoc Analysis of Serial Position in Free Recall (HVLT-R)

The apparent attenuation or absence of the recency effect would seem a rare observation in schizophrenia research, for example, one study compared performance by 62 first-episode participants who were antipsychotic- naïve with 67 healthy controls matched for IQ, age and other variables, on the extensive California Verbal Learning Test (Kristian Hill et al., 2004): deficits were apparent in the schizophrenia group relating to verbal learning, memory, attention and recognition memory; however, no deficits were apparent relating to serial order, i.e. in the primacy, middle or recency portions of the list. Interestingly, the level of negative symptoms was associated with consistency in the recall of items but no other variables and there were no differences between the groups for the rate of forgetting following a 20-minute delay or proactive and retroactive interference arising from the learning of different lists. It was further observed their findings were consistent with other studies with medicated participants with chronic schizophrenia.

A deficit in recency therefore might possibly yield a biomarker of TRS. It may also indicate "an impairment of the phonological short-term store" (see Vallar, 2006 below at p.216). Moreover, on the basis of preclinical studies with rodents (Olney and Farber, 1995; Olney et al., 1999), it is the kind of damage that might be expected to arise from relatively focal damage to the parietal lobe caused by glutamate excitotoxicity, which can arise by various means, but would be also consistent with NMDA receptor hypofunction hypothesis of schizophrenia. It might also offer one explanation of intellectual superiority favouring PIQ in some participants. However, this might conflict with the evident sparing of language comprehension and speech production in the TRS group, as demonstrated by normal performance on the category fluency task, as this might be predicted to be impaired if there is damage in the vicinity of the inferior parietal cortex, including the posterior cingulate and areas proximal to temporo-parietal junction and fibre tracts of the arcuate fasciculus with its different segments (described in Catani and de Schotten, 2010). However, on the basis of DTI and fMRI analysis, it was recently proposed there is a ventral route involving the extreme capsule that connects the middle temporal area with the ventrolateral prefrontal cortex and enables the mapping of meaning to sound, complementing the dorsal route which

might be at greater risk under this scenario (Saur et al., 2008; Hickok and Poeppel, 2004; Makris et al., 2009). The dorsal route may specialise in conveying "sub-lexical" information, "mapping sound to articulation" and complete disconnection of this pathway may result in conduction aphasia where it is not possible to repeat words but is possible to produce unintended utterances and meaningless sounds (i.e. paraphasias and "word salads"), however, it is proposed here that more subtle phonological impairment might be possible including defective or inefficient phonological encoding or storage which would undermine the usefulness of recency.

Yet the HVLT-R was not designed to examine recency and it is necessary to consider alternative explanations, one possibility might be that participants exhibited behavioural inflexibility or inefficient strategies, which Kristian Hill et al. (2004) noted has been observed in the schizophrenia literature. For example, some participants may have preferred to learn and reproduce list items in the same order as they were presented, despite the instruction that items could be recalled (consistent with this, there is a hint of a recency effect around the fifth item in Figure 3. 7, a typical limit for STM capacity, e.g. Miller, 1956; Cowan, 2001). Moreover, they did not change strategy when the list was repeated. However, the summary of frequencies with which the first three words were recalled in the order of their list positions in Table 3. 10 indicates serial recall was not a common strategy.

Possibly a more effective challenge to the proposal that the recency effect was attenuated in the TRS participants, may come with the characteristics of the words in the test list. In particular, it begins with the low frequency word 'Lion', however, this is also acquired early in the childhood lexicon and so is more likely to be recalled (Morrison et al., 1992). The majority of individuals (66.7%) started recall with this word, so perhaps, primacy plus early age of acquisition were sufficiently salient to focus attention upon the start of the list, although, this is not necessarily a refutation of the lack of recency as the last two or three words should still have been available in a transient auditory store.

The area associated with phonological store in the inferior parietal lobe and left temporo-parietal area (Baddeley, 2007; Warrington, Logue, and Pratt, 1971) is also proximal to the posterior cingulate cortex, an area revealed in preclinical rodent studies to be exceptionally vulnerable to glutamatergic damage. Applying a glutamatergic hypothesis, such a deficit might have been predicted in TRS because of preclinical studies which helped to inform the second hypothesis that cingulate gyrus may be implicated, for example, damage was demonstrated to occur in the posterior cingulate at a lower dose of NMDA receptor

antagonist than other areas affected by "a neuron-necrotizing reaction" (Olney and Farber, 1995). Further, in Olney et al. (1999):

Multipolar and pyramidal neurons in the occipital cortex were also susceptible to degeneration, along with "At risk populations" which included "pyramidal and multipolar neurons in the prefrontal, posterior cingulate and retrosplenial, occipital, temporal, parietal, entorhinal, perirhinal and piriform cortices and in the anterior olfactory nucleus, taenia tecta, amygdala and hippocampus. (p.525)

In a "festschrift for cognitive neuropsychology", Vallar (2006) observed "A defective recency in free recall of auditory-verbal lists is a hallmark of the impairment of the phonological short-term store" (p.141) Auditory presentation might have been expected to "load" the phonological loop/ store automatically (Baddeley and Hitch 1974), but just as Vallar (2006) also observed "There may be no advantage in rehearsing items held in a damaged store", recency might not have been used as a strategy because it was not generally helpful. This could have something to do with the quality of encoding in this modality. Selective impairments in auditory verbal short-term memory (Warrington, Logue, and Pratt, 1971) may be rare but more subtle auditory perceptual deficits could be associated with damage to the parietal lobe. Alternatively, deficient sensory gating, possibly linked to abnormal GABA levels, might offer an explanation for subtle perceptual deficits and inefficient encoding.

4.2.10 Might visual learning/short-term visual memory involve "activated LTM"?

The proposal that the short term retention of words and morphemes can rely upon the temporary represented crystallised knowledge might be regarded as "activated LTM". There was corresponding correlation between spatial span scores (a putative measure of the visuo-spatial sketch-pad). However, this may be more difficult to understand with the abstract visual stimuli in the BVMT.

Certainly, a verbal strategy might be applied to some stimuli as they are composed of geometric shapes which could be associated with spatial locations, or perhaps, given labels according to passing resemblance to objects, however, the test was presumably designed to minimise these strategies. One possibility that the association between visual learning and verbal learning is mediated by fluid intelligence (which seems quite possible given the strength of correlations between PIQ and verbal span, between visual learning and verbal span and between visual learning and PIQ (Table 3. 9).

Alternatively, it is suggested here, short term visual learning could be related to "activated LTM" at the level of "elements" of "micro-features" possibly represented in connections between assemblies of cells in the visual association cortex.

4.2.11 Testing the correlations: were negative symptoms associated with correlates of attention rather than higher cognition?

Figure 3. 3 and Table 3. 19 indicate the presence of a small group of VIQ>PIQ individuals could act as a confound in the data. (This was also evident in Figure Appx. 5. 5 depicting correlations involving asymmetry between WASI subscales and proposed markers of attention (CPT-IP and 0-Back SDs) where it can be seen on the right-hand side the four VIQ>PIQ individuals are acting as a polarising influence. (Also see Table Appx. 5.2).

Some post hoc correlations were explored on a reduced set of participants that excluded the four VIQ>PIQ individuals. The overall observation was that the removal of this group weakened some correlations and strengthened others, however, they mostly remained significant or acquired significance. A signficant negative correlation between negative symptoms and VIQ disappeared in the reduced set, possibly because the VIQ>PIQ group had been a polarising influence since they had a low level of negative symptoms and high VIQ scores. The weakening of correlations in the reduced set in several instances (see Table Appx. 5. 2) might be explained by reduced power. However, some correlations were considerably more significant in the reduced set, for example, symbol coding and verbal learning which correlated positively with PIQ, while the percentage of omission errors correlated negatively with VIQ only in the reduced set. Similarly, a negative correlation between trail making and PIQ was significant only in the reduced set.

The most striking correlation to newly acquire significance in the reduced set was a strong positive correlation between the CPT-IP and PIQ, with a large effect size so that better performance on this measure of sustained attention/vigilance was associated with higher PIQ scores (VIQ>PIQ individuals had marked decrements in their PIQ scores). Similarly, an inverse correlation between another putative marker of sustained attention, 0-Back SDs with PIQ was significant only in the reduced set, again with a large effect size. Therefore, correlations between the attentional markers of CPT-IP score and 0-Back SDs with PIQ appear to have been confounded by the presence of 4 VIQ>PIQ individuals who performed well on attentional measures yet had relatively poor performance IQ. As noted above, the inverse correlation between negative symptoms and VIQ was only significant in the full set

(Table 3. 18, p.161 compared with Table Appx. 5. 2, p.360), while there were no significant correlations between negative symptoms and PIQ in the full or reduced set of participants. From this it might be inferred higher PIQ scores (and, perhaps, by extension fluid intelligence) were associated with the better application of attention; however, the absence of a correlation between PIQ and negative symptoms which correlated with other variables associated with attention (Table 3. 17, Figure 3. 11) is worth noting. Apart from the inverse correlation between negative symptoms and VIQ which depended on the presence of the VIQ>PIQ group, it would seem that negative symptoms were generally associated with putative markers of attention rather than higher cognitive functions. This was supported by a lack of significant correlation between negative symptoms and the tests on the MCCB, whether in the full or reduced sets.

Consistent with this interpretation, the only exception was a strong negative correlation between negative symptoms and performance on the test of sustained attention/vigilance (CPT-IP). While there was the very strong correlation been CPT-IP with PIQ that emerged in the reduced set, negative symptoms and 0-Back SDs still did not correlate with PIQ. These associations may be mediated by different biological factors as it is observed that the CPT-IP is a test of selective attention as well as sustained attention (whereas, it is proposed that the simpler 0-Back condition may be a purer test of sustained attention). As selective attention requires the inhibition of distractors (which may be perceptual or occurring at higher levels of representation), neuromodulators such as dopamine and GABA could be more effective in the 0-Back condition as there is less perceptual load and the pace of presentation is slower than in the CPT-IP.

However, to consign negative symptoms to an attentional factor that has little bearing on higher cognitive function could be a mistake, since the presence of negative symptoms are associated with worse functional outcomes (Rabinowitz et al., 2012), also they may have been generally too low in this group to have an influence. Moreover, an association between negative symptoms and the sensory gating of visual information has been observed in studies using backward masking where it has been observed that longer periods may be required for the processing of early visual information in schizophrenia (Herzog and Brand, 2015; Greene, 2007; Shaqiri et al., 2015). Interestingly, in the latter study, nicotine was observed to ameliorate age-related deterioration in backward masking. It has been further proposed an imbalance in the GABAergic system might underlie these "gamma oscillations in the somatosensory cortices may be associated with the SG [sensory gating] ability and behavioral performance of response inhibition" although the evidence base is currently weak (Cheng et al., 2016, p.20437). However, it would seem clozapine has the potential to

improve this through actions at D4 receptors which are highly concentrated in the hippocampus (Andersson et al., 2012).

However, it should be considered that the CPT-IP was not tested on a TRS population, along with the incidental observation that some participants complained they felt uncomfortable (one mentioned “flickering”). Clozapine has been reported to improve sensory gating deficits (Micoulaud-Franchi et al. 2015) but the difficulty observed in this study could indicate problems may persist even after clozapine treatment has commenced. Alternative explanations include undetected problems concerning the computerised display or lighting conditions, however, as observed in the introduction, perceptual deficits have been frequently observed in schizophrenia yet appear to be routinely overlooked. It is proposed that early sensory deficits could have a profound effect on signal detection and the quality of subsequent encoding. This is turn might affect the trade-offs between processing and capacity. This is a different kind of hypothesis (although not a mutually exclusive one) from the initial one that proposed hyperactivity in the DMN (or a preoccupation with the “inner world”) might be related to negative symptoms which, in turn, might cause microlapses in attention, discussed in the next section.

4.3 The Neuroimaging Study

4.3.1 Hypotheses

The main hypothesis of the fMRI study was that TRS participants would, during the performance of a verbal n-back task, show attenuated activation in a fronto-parietal network similar to that described for healthy controls in previous studies. The second hypothesis was that brain areas exhibiting altered haemodynamic response would include the cingulate gyrus and would be associated with task performance and symptom severity. That hypothesis was informed by emerging evidence that a dopaminergic theory involving hyperactivity in the striatum may be an unlikely candidate for the aetiopathology of TRS, rather a glutamatergic hypothesis might provide a better account. The early seminal papers in this area are based on preclinical studies by Olney and colleagues which were specifically motivated by the problem of persistent negative and cognitive symptoms after more florid positive symptoms have resolved and therefore seem particularly pertinent to TRS.

These highlighted the physical vulnerability of various areas in the rodent brain to glutamate excitotoxicity consequent upon antagonism at the NMDA glutamate receptor causing transient reactions or more permanent cell loss but without pathological hallmarks such as glial scarring (see Najjar & Pearlman, 2015; Vostrikov et al., 2007, 2008). The most vulnerable areas appeared to involve midline structures including the cingulum, but perhaps especially the posterior cingulate. Further, clozapine was demonstrated to prevent these effects (Olney and Farber, 1994, 1995; Olney et al., 1999). While there are profound differences between the rodent and human brain, if demonstrated in the human brain, a pathological focus involving the cingulum and perhaps the corpus callosum inferiorly may have functional consequences for large-scale networks.

4.3.2 Results of factorial analysis

The results of factorial analysis revealed that the group with the higher level of pathology (TRS participants relative to controls) displayed attenuated haemodynamic responses with increasing cognitive load. In the factorial analysis concerning the TRS and control participants, these were observed in the in the right middle frontal gyrus, left superior frontal gyrus, right thalamus, left middle temporal gyrus and parahippocampal gyri bilaterally, the right parietal lobe, right precuneus and left lingual gyrus (Figures 3.22, 3.24, 3.25, 3.27).

A consistent pattern of attenuation was also observed concerning decreases in the haemodynamic response with increasing cognitive load in the TRS group. These decreases are described as increases in the haemodynamic response as this is relative to the control group which exhibits progressive decreases in the haemodynamic response with increasing cognitive load. Significant contrasts were observed in in the left medial frontal gyrus, and left superior frontal gyrus, the left anterior cingulate, right putamen, left cingulate gyrus (posteriorly), left paracentral lobule. In the figures depicting these, there often appears to be little or no change from the baseline as cognitive load increases in the TRS group (Figures 3.20, 3.21, 3.23, 3.26). These contrast with the progressive reductions in the haemodynamic response observed in the control group in the same figures.

Similarly, in the factorial analysis concerning the higher PANSS and lower PANSS groups, the higher PANSS group exhibited an attenuated increase in the haemodynamic response with increasing cognitive load in the left claustrum, left middle frontal gyrus, left inferior frontal gyrus and left supramarginal gyrus (Figures 3.29, 3.31). While an increased haemodynamic response was observed in the left superior frontal and right medial frontal and right postcentral gryi, where, a marked attenuation relative to the baseline task, was again observed in higher PANSS group (Figure 3. 30). The right postcentral gyrus in the parietal lobe exhibited the largest cluster size (482 mm3) in this factorial analysis and so might be implicated in DMN activity (Table 3. 25). While the relatively smaller clusters (57 mm3 and 50 mm3) in the left superior and right medial frontal cortex might be described as the DLPFC (BA 9), the medial location of the clusters suggest they are part of the medial prefrontal cortex, bilaterally, which is consistently identified as core node in the DMN.

4.3.3 The implication of connector hubs in large-scale networks

In addition to the consistency of the pattern and widespread nature of the foci, a further striking aspect of the contrasts between control and TRS participants is that all the areas (at the subcortical as well as cortical level) appear to be important hubs for information processing that have been identified through graph theoretical approaches applied to structural data (e.g. from DTI) and functional MRI. Hub areas are characterised by having a high number of connections with other highly connected hubs (forming "rich clubs") and other nodes in the network. They also exhibit high "betweenness centrality" and shorter path length. As summarised by Bullmore and Sporns (2012), an important aspect of this topological organisation is to facilitate communication between areas in a parsimonious way which minimises "wiring costs" as from a metabolic perspective, long range connections between nodes whether structural or functional, are expensive to build and maintain. They are also likely to be heavily myelinated in the mature brain as maintaining ion gradients across membranes involves a high degree of energy expenditure.

Moreover, at the cortical level, there is also very considerable agreement between the areas of differential activation in this study with those areas identified by Fornito et al. (2011), in a twin study of resting state connectivity, as areas having a high degree of heritability. Long range connections enable integration across specialised modules, as typically required by higher cognitive function, but in view of their "wiring cost" it is hypothesised that evolution will only favour connections which have proven adaptive value. These arguments are presented in Bullmore and Sporns (2012), who also present an image from Fornito et al. (2011) showing areas of high heritability.

The TRS group exhibited heightened activity in the default mode network, and the resulting dominance might present an ongoing source of distraction during the performance of the n-back task, resulting in microlapses in attention and contributing to longer and more variable latencies in the clinical group. This idea is highly similar to one about behaviour between networks advanced by Kelly et al., (2008). Such a habitual state might also weaken some connections while strengthening others making it more difficult to disengage the DMN and possibly to avoid an impasse, it may be necessary to be able to shift attention between networks by various mechanisms (apart from the usual desirability of having duplication or redundancy in systems in case one element should fail).

The default mode network was identified only fairly recently, first using PET (Raichle et al., 2001) and then resting state methodologies (Greicius et al., 2003) and is defined as a set of areas that are more active when an individual is resting with eyes closed or engaged in inwardly oriented activities such as planning or day-dreaming. This has lead to a pardigm shift, closely followed by theories about communication across and between large-scale networks through oscillatory rhythms (Raichle, 2009; Buzsaki and Freeman 2015).

Subcortically, the thalamus has long been recognised as an important relay hub in striatal circuitry. Not only does it relay information from cortical areas, but it also sends information from the cerebellum, brainstem, autonomic and endocrine systems. As part of the striatum, the right putamen also has an important role in relaying information (van den Heuvel, & Sporns, 2011).

Helpfully, in this study all but one TRS participant, successfully performed the n-back task at the highest level of cognitive load. Also, significant differences between the TRS and the control group only emerged when factorial analysis included the highest level of cognitive load. This may help to explain the continued dearth of studies on TRS, as previously mentioned, Nakajima et al., (2015) found only 5 studies comparing TRS and with healthy controls, of which only one was an fMRI study (by Fitzgerald et., 2007, involving 3 participants described as having treatment resistant auditory verbal hallucinations).

This study further highlighted significant differences between the lower and higher PANSS groups even though the range of symptom scores was fairly limited. Important connector hubs areas were again apparent. The higher PANSS group exhibited an attenuated haemodynamic response with increasing cognitive load in the left claustrum and left frontal gyrus relative to the lower PANSS group (Figures 3.29, 3.31), as well as an increased haemodynamic response in left superior frontal, right medial frontal and right postcentral gyri (Figure 3. 30). These results show a common pattern in the haemodynamic response in all the contrasts – that of stronger activation or deactivation relative to within group baselines in the control group relative to the TRS group and, similarly, in the lower PANSS group relative to the higher PANSS group. This is interpreted as indicating pathology or higher pathology may result in an attenuated response.

Of particular interest is the left claustrum with a peak which appears near fibres of the anterior limb of the internal capsule. This has extensive long-range functional connections with virtually every part of the brain, however, it rarely appears as an area of differential activation in the literature, possibly, because it may be difficult to distinguish from other

structures with which it may co-activate and also by virtue of its long, thin shape. The extensive connectivity and proximity to the key nodes of the salience network (insula and anterior cingulate cortex) could provide an important compensatory function in the lower PANSS group by helping to support activity in other areas (also see 4.3.5 below).

With respect to networks, it is apparent that apart from areas associated with particular task positive activities such as the premotor area BA 6, and the cognitive control network characterised by interactions between frontal and parietal areas, the major nodes of the DMN, including the medial temporal lobe network appear to be present (Andrews-Hannah et al. 2010; 2014).

The pattern of attenuation has many potential explanations, some of which are compatible with the literature in schizophrenia such as impaired connectivity and glutamatergic theories. However, simpler explanations may also apply involving artefacts or side effects of medication with clozapine. However, as there is a dearth of literature in this area and a virtual absence of peer-reviewed neuroimaging studies, this study is largely exploratory and perhaps its value may lie in the generation of hypotheses of which there are several.

One explanation for the observed haemodynamic patterns could lie with glutamate NMDA receptor hypofunction on GABAergic interneurons as Anticevic et al. (2012) observed similar attenuation in selected areas following the administration of the glutamate receptor antagonist, ketamine, in healthy volunteers. As previously mentioned (section 1.5.2) ketamine may exacerbate or reinstate symptoms in schizophrenia (Krystal et al., 1994). Also, in Honey et al. (2008) a high dose of ketamine induced negative symptoms in healthy individuals. Further, marked alterations in the fMRI response in fronto-thalamic circuity were observed when ketamine was administered at a lower dose: with an increase in activity in the thalamus, bilateral caudate and right putamen.

There may be further compatibility here with a resting state connectivity study of 250 healthy individuals by Manza et al. (2015) who observed the putamen, along with the pallidum exhibits negative connectivity with key nodes in of the DMN (posterior cingulate and ventromedial prefrontal cortex), and so anticorrelation which was interpreted as supporting the “task positive network” (which includes the somatomotor cortex), which declined with age. (This is reminiscent of Marsman et al.’s (2013) meta-analysis on glutamate deficits in PSZ which exhibited acceleration with age).

Observations of abnormal glutamate function in TRS individuals do, of course, invite consideration of TRS in terms of glutamatergic theories, perhaps, especially when the case for a dopaminergic one is unclear (although of course, shared or inter-related circuitry may be involved). Convergent evidence of potential glutamatergic damage within this study, might be found in the observation of a lack of a recency effect in immediate free recall in the post hoc analysis of performance by TRS group in the HVLTR, as discussed in section 4.2.9 above. This theorising around glutamatergic theories is highly speculative, however, further indirect support could come from functional connectivity resting state studies (possibly the only ones of TRS to date) by Wang et al. (2015) and Ganella et al. (2017, 2018). Both observed decrements in connectivity in TRS individuals relative to controls and Wang observed some unique connections that were specific to unaffected first-degree relatives that were not present in the control or TRS group and so were proposed to be potentially compensatory. However, it was the increases in local efficiency which were interpreted as a possible compensatory strategy by Ganella et al. (2018) that might be deployed in a different argument as it was accompanied by decrease in global efficiency: the local increase would be predicted to arise in the event of disruptions to large scale networks as a result of topological reorganisations to optimise the organisation of the brain with respect to the brain's "energy budget."

However, there are other explanations for the observed pattern of attenuation. Energy deficits of another kind, for example, arising from a thyroid hormone deficiency (not uncommon in psychiatric populations). A more likely factor in this context might be the development of a degree of insulin resistance as a side effect of clozapine (hyperglycaemia is a common side effect). Hyperactivity in the DMN has been observed in the context of metabolic disorders e.g. Cha et al. (2015). Similarly, anything else that might compromise energy might be expected to affect core hubs and attenuate activity, for example, drowsiness can be caused by clozapine. Moving on to the realm of potential artefacts that might give the appearance of attenuation, the groups were not matched for IQ and so, while the TRS individuals exhibited normal estimated IQ scores overall and included some very high functioning individuals, this data was not collected for the control group.

A further possible limitation is that errors were not modelled in the analysis in the interests of conserving data, nor were d'prime values used. Fortunately, the error rates were very low in the control group and also in the TRS group with most errors occurring on the second trial of the 3-Back condition, which is interpreted as indicating participants were trying to perform the 3-Back task although their strategy was less successful at that point. A more detailed consideration of all the above will follow.

4.3.4 The Insula and Anterior Cingulate Cortices

Maintaining a rostral focus, linear trend increases were observed with increasing cognitive load in the insula (BA13) in the right hemisphere in the control group, and in the TRS group bilaterally (the co-ordinates of the peak maxima in the left insula were highly similar to those for the left caudate body). The insula which is recognised for a role in interoception is also a key node of the salience network along with the anterior cingulate cortex. However, an increase in the ACC with increasing cognitive load was not observed in either group, although a sizeable area of deactivation (708 voxels) was observed in the TRS group (Table 3. 23) but not in the control group. This could potentially reflect a failure in the monitoring function of the ACC at more difficult levels of load in the TRS group.

It would be wrong to assume the ACC is not activated during performance of the baseline task as there are still speed/accuracy trade-offs to be made, so decreasing activity with increasing cognitive load could reflect a fatigue effect or, possibly, the irrelevance of ACC activity at more difficult levels of the task in TRS individuals, so it might fall away on the basis this is an ineffective use of resources. A similar argument was used by Callicott et al., (2003), when they observed an inverted-U of activity in the DLPFC as the capacity of working memory was exceeded. Consistent with this, individuals with schizophrenia who exhibited superior performance also demonstrated increasing activity in the DLPFC like controls rather than exhibiting "hypofrontality" that had been widely described. However, there are no significant within group activations above baseline in either group in the tables of Appendix 2, so the "falling away" argument seems unlikely in this instance.

An alternative idea to this last proposal is that there is a deliberate suppression of activity in the ACC with increasing cognitive load because this provides a source of distraction, perhaps, even more so if it is bilateral. This seems possible given the "alerting role" ascribed to the salience network as proposed by Menon and Uddin (2010) who proposed the networks responds to the "bottom-up" detection of salient events and facilitates the efficient allocation of cognitive control and attention. This may involve rapid switching between large-scale networks (e.g. between "task positive" and DMN activity). It may also require the rapid mobilisation of motor responses as reflected in a strong functional coupling between the ACC and motor cortex. Therefore, it seems plausible, if there were a lack of selectivity in the salience network this might interfere with the efficient deployment of attention and processing resources. This could be consistent with observations of hyperactivity in the ACC in TRS (Mouchlianitis et al., 2016 (a), except that most of the TRS

participants in this study had been medicated with clozapine for a long period and it is proposed elsewhere in this thesis this may have helped to "normalise" neural activity.

4.3.5 The Claustrum

A linear trend of increasing activation with cognitive load was observed in the left claustrum (anteriorly) in the control group, but not in the TRS group. The rostral locus of this cluster suggests a proximity to other structures engaged in higher cognitive processing as, in the "economy" of the brain's organisation, such relationships may not be coincidental (Bullmore and Sporns, 2012).

The claustrum is a subcortical structure that is connected with virtually every part of the cortex. It is packed with GABAergic parvalbumin-positive interneurons and claustral projection neurons. However, synaptic connections between the latter are rare, suggesting it may be unsuited to integrating multisensory information within the claustrum (Kim et al., 2016, p.781). Rather, they suggest this architecture may be sensitive to correlated inputs and so may respond to novelty. It may also amplify activity. This is consistent with proposals that the claustrum may detect fairly non-specific but salient changes in the external environment (Remedios, Logothetis and Kayser 2014); also see Goll et al. (2015), who observed claustral neurons appear especially responsive to step-wise changes in sensory inputs. Goll et al. (2015) further proposed the claustrum could help to "decide" between competing activations in different cell groups, possibly in different modalities, that are demanding attention. It is suggested here that all these features may enable the claustrum to modulate the signal, for example, by decreasing interference and possibly enhancing other aspects during the performance of the n-back task (also see correlation with 0-Back SDs, Figure Appx. 6. 4). Therefore, it might help the integration of information but through activities beyond the structure of the claustrum itself. This is compatible with Meletti et al. (2015) that the claustrum is a "highly relevant hub centre in neural synchronization of several (and distant) cortical areas" (p.1230) As such it can "potentially bind together and modulate neural activity". However, the lack of significant activity in the claustrum in trend analysis for the TRS group might suggest that either participants could not perform the highest level of the task (it is suggested the error data does not support this interpretation), or perhaps, the long-range connections intercepted by the claustrum are less effective. This may be consistent with the proposal that the communication and integration of information across long range connections may be compromised in TRS, although, as explored in the introduction there may be numerous ways this might arise.

4.3.6 Other Middle and Superior Frontal Areas

In the TRS group, apart from BA9, clusters of significant linear activation were also observed in middle frontal gyrus bilaterally, described as Brodmann area 10. A further cluster was observed in BA8 in the superior frontal gyrus in the right hemisphere. All these areas are considered to be part of the prefrontal cortex. Increasing activation was also observed more posteriorly in the premotor cortex in the right BA6 (middle frontal gyrus), and left BA6 (precentral gyrus and in a proximal sub-gyral location). These latter activations may have been related to motor activity, for example, even a simple action might require more cognitive effort because of the need to inhibit responses to distractor stimuli held in working memory; or perhaps, because of more general depletion of resources associated with meeting demands associated with higher levels of cognitive load.

In both groups, sizeable clusters, also in BA6, were observed with peak maxima in the longitudinal fissure and described as the medial frontal gyrus, which is an important hub in the DMN. In the control group, this was ascribed to the right hemisphere, and in the TRS group to the left hemisphere. However, a linear increase in activity in the medial prefrontal cortex with increasing cognitive load is at odds with classical descriptions of DMN activity (Fox et al., 2005), so this activation is perhaps more compatible with the BA6 designation, but it might also reflect the supplementary motor area (SMA) which has a more medial location within BA6 and is superior to the dorsal ACC. The reliability of activation in the right SMA (regardless of the sensory modality of a stimulus) with co-activations in the right temporal parietal junction, the inferior frontal gyrus, anterior insula and anterior cingulate led Corbetta and Shulman (2002) to propose a ventral-fronto-parietal attentional system based in the right hemisphere which processes "bottom up" information and has an alerting role which may interrupt processing under the control of more consciously directed attention. However, evidence from intrinsically defined networks has since indicated the SMA may be involved in the bilateral "top-down" dorsal attention system (Fox et al., 2006). What is clear, however, is that the premotor cortex and SMA (BA6), the dorsal ACC and DLPFC have been shown to be typically activated in the within group analyses of executive tasks, including the n-back (Minzenberg et al., 2009).

4.3.7 The Medial Prefrontal Cortex ("proper")

While the labelling of clusters in BA6 has been questioned above, this is not the case for those described as the medial prefrontal cortex showing a negative linear trend in activation in the left BA8 (Table 3. 23) and left BA10 (Table 3. 21) in the TRS and control groups

respectively. These relative deactivations are consistent with classic descriptions of DMN nodes (Raichle et al., 2001; Andrews-Hanna et al., 2010); for example Fox et al. (2005), classically described the DMN as involving *decreasing* activity in a "set of regions, including posterior cingulate, medial and lateral parietal and medial prefrontal cortex" (p.9673) during cognitive tasks which are demanding of attention.

4.3 8 Broca's Territory

As sub-vocal articulatory rehearsal might be expected to support successful performance in the n-back task, it might be predicted that trend analysis would also reveal increasing activation in Broca's area (BA44, and BA45, in the dominant (left) inferior frontal gyrus). However, neither area was significant in the TRS group, while activity in a relatively small cluster with a peak maxima lateralised in the right inferior gyrus (BA 9) in the control group seemed an unsuitable candidate as the participants were right-handed. However, the lack of significance in the trend analysis may not be anomalous because in meta-analyses of executive function involving healthy individuals, or those with schizophrenia (Owen et al., 2005; Minzenberg et al., 2009), Broca's area rarely achieves prominence, although this may be present in individual studies e.g. Chen and Desmond (2005).

4.3.9 Wernicke's Territory

Similarly, Becker et al., (1999) questioned the assumption that a phonological store supporting working memory might be localised to the supramarginal gyrus (BA 40) in the vicinity of Wernicke's area and the angular gyrus (BA 39) in the dominant hemisphere. Inconsistent or weak observations might in part be explained by difficulties in localising activity in areas subsumed by large clusters; also more recently, tractography studies have shown fibre tracts with terminations outside the language areas they classically link, which is why Catani and Thiebaut de Schotten (2012), prefer to use the term "territory" when referring to Broca's and Wernicke's areas. Further elucidation of the circuitry has been provided by Fegen et al., (2015) who concluded the middle frontal cortex and the superior parietal lobe respond to load in verbal working memory (observations which hold for both groups in this study). Additionally, they identified activity in a circuit involving a parietal-temporal area around the Sylvian fissure which showed linear load effects but was also affected by rehearsal rate. The nodes in this circuitry included the inferior frontal gyrus, possibly corresponding to Broca's area, the premotor cortex and parietal areas - superior parietal lobule and BA7.

In these analyses, linear increases in activity with increasing cognitive load were observed in both groups in the right supramarginal gyrus (BA40), the right precuneus (BA19), the left inferior parietal lobe (BA40) and left precuneus (BA7). These areas may be linked with the area of activation in the temporal lobe inferiorly by the arcuate fasciculus which has a rising middle segment. According to Catani and de Schotten (2012) p.241, the terminals of this pathway (which is also bundled with a long segment) extend beyond the classical language areas, including tracts within the middle temporal gyrus, i.e. beyond the confines of BA 22 which is traditionally attributed to Wernicke's area, also beyond BA 44 and BA 45 which form Broca's area, with terminations in the posterior middle frontal gyrus and inferior precentral gyrus. Accordingly, increasing activity in these areas may reflect the engagement of circuitry associated with language processing and memory.

Possibly consistent with the above, trend analysis also revealed linear decreases in activation in with increasing cognitive load in the right transverse gyrus (BA 41) in both groups. This is primary auditory cortex, also known as Heschl's gyrus. As all participants were right handed this increased the likelihood that language would be left lateralised, However, arguments based on lateralisation may be confounded through enrichment by other sensory associations: from lip-reading to orthography; also, by the level of processing: from syntactic analysis of the "speech envelope" to the fine discriminations required for phoneme analysis. All that will be ventured here, is that the progressive diminuation of activity in the contralateral hemisphere might decrease interference during phonological processing.

4.3.10 The Precuneus

The role of the precuneus is far from understood and as with its neighbour, the PCC, it is likely to be very important because of its position in a highly protected area within the medial fissure and towards the back of skull (where it slopes) so is less likely to suffer damage during a fall. Consequently, there has been a death of neuropsychological case studies to advance understanding. However, there appears to be broad agreement the precuneus has a high degree of connectivity with another highly protected area, the posterior cingulate cortex (Leech and Sharp, 2014). This has led Andrews-Hanna et al., (2014) to describe this area as "the broader PCC" which they propose is an important zone of integration supporting bottom-up attention to behaviourally relevant sources of information drawn from memory and/or perception)." While Fransson et al. (2008) observed "the precuneus/posterior cingulate is the only node in the default mode network that directly interacted with virtually all other nodes."

The precuneus is known to be a projection target for serotonergic neurons and highly interconnected with other brain areas (Castellanos et al., 2008) and is accepted by many as an important node in the default mode network along with the adjacent posterior cingulate cortex inferiorly and the medial prefrontal cortex which is also a notable target of serotonin innervation. The precuneus and the posterior cingulate cortex are linked by long range connections to the anterior cingulate cortex (Castellanos et al., 2008). All these areas are implicated in the pathophysiology of schizophrenia.

The precuneus also emerged as an area that correlated with the haemodynamic response in some BBAMs, for example, in the TRS group (Table Appx. 6.3) there were negative correlations between the haemodynamic response in the right precuneus (BA 31 and BA 7)[55] and the proxy variable of attention (SDs in the 0-Back condition), with greater activation in the 2-Back and 3-Back conditions being associated with better attention (indicated by lower mean standard deviations, as depicted in Figures Appx. 6.6 and 6.9). Only three higher PANSS participants had values below the TRS group median 0-Back SDs. In this analysis it was also interesting a negative correlation was observed in the claustrum in the 1-Back condition, another highly connected structure, that may have been performing a similar role to the precuneus. At the highest level of cognitive load, a further negative correlation was observed with the medial frontal gyrus (BA 10), an important node of the DMN and, as mentioned above, a target for serotonergic innervation. Taken together, these results suggest better attention/ cognitive control was associated with increases in the haemodynamic response relative to baseline in these important areas of the DMN. Similarly, in the corresponding BBAM correlation for the control group , there was a significant negative correlation in the haemodynamic response involving the right precuneus (BA7) in the 2-back condition with 0-Back SDs. However, this was not significant at the 3-Back level (Table Appx. 6. 4).

[55] This variation in labelling may not be troubling as this area lacks a distinctive cytoarchitectural boundary between the the mesial precuneus of BA7 and BA 31 - the latter being described by Cauda et al., (2010) as a transition area between BA 7m and BA23c. Cavanna and Trimble (2006) elaborate further, describing a gradually changing gradient (in a rostro-caudal direction): the *medial* surface of the precuneus has fully differentiated isocortex with prominent layers 11, 1V, V and V1 and a columnar organisation, whereas the precuneus more mesially, the retrosplenial and posterior cingulate cortices are thinner. The resulting diversity of the cytoarchitecture may also reflected by extensive cortical and subcortical connections, accompanied by the fractionation of this area into several subdivisions.

To summarise, negative correlations were observed between activity in the right precuneus in the control group during the 2-back condition and in the clinical group in the 2-back and 3-back with a proxy measure of attention. Less responding variability in the baseline task was associated with greater activation in these areas.

There may be some hazard related to using a proxy variable that will also correlate indirectly with the neural activation in the experimental condition because it is likely to be related to the baseline neural activations from which the experimental activations are subtracted. However, an investigation of standard deviations and/or reaction times may also be warranted because responses in the TRS group were slower overall and this could impact upon the fMRI BOLD signal markedly. Parasuraman and Jiang (2012), for example, observed less neural activation in executive function paradigms in healthy individuals who were fast and accurate compared to those with slower and made more errors. In one comparison between individual participants, increased activity could be partly explained by the further engagement of areas associated with conflict monitoring (the anterior cingulate), default mode activity (posterior cingulate) and areas associated with emotional regulation (subcortical limbic areas). In another experiment with 30 healthy participants, they observed less activity in the precuneus in participants with superior performance - a result which contrasted with heightened activity in the precuneus that has been observed in clinical populations (Buckner, Andrews-Hanna and Schacter, 2008). This pattern is consistent with an interpretation that equates slower and more erroneous performance with distraction, or, alternatively, weaker application to "task positive activity" due to hyperactivity in the default mode network. It may also find some resonance with the observations in Honey et al. (2000) who observed in a verbal n-back study that healthy participants with slower reaction times also activated areas in the posterior parietal cortex bilaterally (although the Talairach co-ordinates were not similar to those reported here). The co-ordinates for the precuneus in the TRS and controls in the correlational analyses with 0-Back SDs in the 2-Back condition were more similar at x = 25, y = -67, z = 20 in the TRS group and x = 25, y = -59 and z = 30 in the control group, even though they were labelled as BA 31 and BA 7 respectively (Tables Appx. 6. 2 and 6. 4).

The replication between groups and across task levels of the negative correlation between activity in the right precuneus and mean SDs in the baseline task suggests it is robust and its presence at the more difficult task levels could indicate it is related to bringing more processing resources to the task or, perhaps, suppressing other areas of the DMN. An alternative explanation for the absence of this correlation from the 1-Back condition, might

be due to a higher indirect correlation between this proxy variable (which may index inattention) and baseline activity in the 1-Back condition which is subtracted from the 0-Back condition to produce the SSQ values. However, this seems less likely as there is another significant negative correlation 1-Back condition in the control group (where reaction times and standard deviations in the baseline task had identical ranks): the left transverse temporal gyrus (primary auditory cortex, Heschl's gyrus) which, at first sight, has a more tenuous relationship with attention or default mode activity. This correlation could reflect individuals in the control group responding to the phonological aspects of stimuli, either as an epiphenomenon (possibly detected because the signal is more discernible in this group), or as a verbally mediated strategy in the 1-Back task that assists performance.

If the negative correlations between the right precuneus and average of standard deviations in the baseline task are not artefactual, this is actually in the opposite direction to what might be predicted as default mode activity generally anti-correlates with tasks which require engagement with the outer world and decreases further with increased task demands (Greicius et al., 2003; Ceko et al., 2015). It is also contrary to the pattern described above by Parasuraman and Jiang (2012), and Buckner et al. (2008).

A potential explanation may lie with this activity being related to an area of the precuneus (treated by Leech et al., 2011, as part of the PCC), which by virtue of its connectivity acts in a contrary way, has been described by several researchers. Using resting state fMRI, Leech et al. (2011) showed complex interactions involving different parts of the PCC and other intrinsic connectivity networks, for example, the anterior (dorsal) PCC exhibited increased functional connectivity within the DMN and stronger anti-correlation with the frontal parietal attention network with increased task demands. Whereas the posterior (ventral) PCC showed increased connectivity within the DMN when attention was internally directed. In other words, the anterior aspect of the PCC may be involved in suppressing the DMN while requiring it to be active in order to be suppress it, i.e. the DMN may have a role in suppressing itself. The precuneus seemed to be involved in both functions

These observations find considerable resonance with Utevsky 2014, who observed increased connectivity between the precuneus and the right frontoparietal (executive) network during task performance, and heightened connectivity between the precuneus and the DMN during rest. This organisation is also recognised by Cauda et al., (2010) in their rsfcMRI study concerning four areas of the posteromedial cortex: "The dorsal portion [of the anterior precuneus in BA 31 and the PCC in BA23] seems to be functionally associated with the

TPN, whereas the ventral portion, along with the retrosplenial cortex (BA 29 and BA 30), is selectively interlinked with the TNN" (p. e13107)

Utevsky et al. (2014) describe Leech et al., 2011 as offering a "unifying" resolution of competing results, "by acknowledging that the precuneus is functionally variable, exhibiting connectivity with different neural networks according to task state or level of engagement with one's surroundings and demonstrating that connectivity between the precuneus and the DMN reflects this level of engagement" (p.937)

4.3.11 The Temporal Lobes

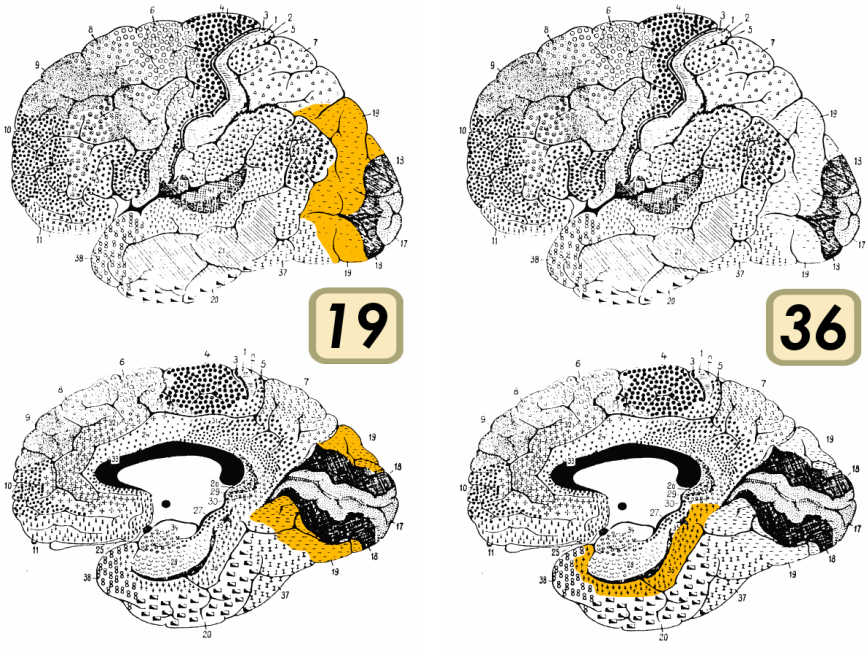
Areas of increasing activation with cognitive load were observed in the temporal lobes with peak maxima in the middle temporal gyrus (left BA 21 and right BA20) in the control group and in the fusiform gyrus (left BA 36) in the TRS group (Table 3. 20). In the trend analysis for the TRS group, the labelling of BA36 as the fusiform gyrus is slightly problematic as it is more usual to ascribe this label to BA37 (which is recognised for involvement in processing facial information), whereas BA36 is an area of dysgranular cortex (lacking layer IV cells), sometimes described as the ectorhinal area and part of the perirhinal cortex.

BA36 (shown in Figure 3. 41 below) appears to be involved in coding recency or familiarity - as discussed by Davachi (2004) who cited studies which have observed a correlation between activation in the perirhinal cortex with item recognition or item familiarity - distinguishing it from activity in the hippocampus which is associated with conjunctive memory (or, "source recollection"). The coding of recency or use of familiarity might also be a more apt considering the nature of the n-back, particularly as performance comes under pressure. On the other hand, a case for the role of the fusiform gyrus in processing aspects of language has been advanced by Mechelli et al., (2000) who proposed the fusiform gyrus may specialise in the processing of local features of visual inputs, while the lingual gyrus (especially, the right medial posterior lingual gyrus) may be involved in the processing of the global features of words and objects, as demonstrated by greater activation during the processing of degraded stimuli such as might be found with reduced contrast). Activation in either area might be expected to support processing during the performance of the n-back. Although the activity was only significant in the TRS group, this could reflect greater reliance on the processing of orthographic features rather than verbal mediation using articulatory rehearsal per se as cognitive load increases (a view that is reinforced by suspicions concerning the usefulness of the phonological store raised in the discussion of the recency effect in free recall (section 4.2.9). By contrast, it may be relevant to note there

was a negative correlation for the control group in the left transverse temporal gyrus (BA 41, Figure Appx. 6. 14) where greater variability in 0-Back SDs was associated with less activation in this area of primary auditory cortex during the 1-Back condition. While there was an opposite positive correlation in the right superior temporal gyrus (BA 38) which is located in the temporal pole (Figure Appx. 6. 11). Its function remains obscure although a meta-analysis of 11 connectivity studies indicated in may be involved in language production and comprehension (Ardila et al., 2014).

The reason for the increasing engagement of the BA19, in the right hemisphere in the TRS group and the left hemisphere in the control group is unclear (Tables 3. 22 and 3. 20). In the analyses it was labelled as the precuneus within the parietal cortex, although BA19 is usually classified as part of the occipital cortex. As can be seen in Figure 3. 41 on the medial surface BA19 is anterior to the cuneus and superior to the lingual gyrus - both areas are involved with visual processing. However, consistent with the peak maxima and the parietal designation, activity in this cluster could related to multimodal integration. On the other hand, the cluster in the control group might be discounted as an artefact as the peak maxima was 10mm away from the nearest gray matter, although this doesn't explain the peak activation in the opposite hemisphere for the TRS group at similar co-ordinates.

Figure 3. 41 Brodmann Areas 19 and 36



By Brodmann - File:Brodmann_Cytoarchitectonics.PNG, Public Domain, https://commons.wikimedia.org/w/index.php?curid=8284855

By Brodmann - File:Brodmann_Cytoarchitectonics.PNG, Public Domain, https://commons.wikimedia.org/w/index.php?curid=8433977

4.3.12 The Cerebellum

In the trend analysis, increasing activation with increasing cognitive load was also observed in the cerebellum bilaterally for both groups. Even though the cerebellum is well-known for its role in movement, it has been implicated in higher cognition for a long time because of neuropsychological studies concerning the effects of focal cerebellar lesions (Ravizza et al., 2006). More recently neuroimaging studies with healthy participants have demonstrated the cerebellum is reliably activated in verbal working memory tasks and this is also seen in the within-group activations at every level for both the control and TRS groups (Appendix 2). Increased activation with increasing cognitive load could simply reflect a greater rate of articulation or phonological mediation. However, a model proposed by Desmond (1998), which found favour with Kirschen et al., (2005), distinguished between processing of articulatory control and phonological storage in superior and inferior cerebellar regions respectively in a WM task. In addition to increases in cerebro-cerebellar activation with increases with cognitive load, they observed increased activity with practice (involving the right inferior cerebellum and left inferior parietal lobe), which might instantiate improvements in attention/ attentional control/ application of attention. Therefore, it does seem likely that not only does the cerebellum support higher cognition, but function may also segregate with different areas. Certainly, different parts of the cerebellum are associated with significant activations in these analyses but as the cerebellum has numerous divisions, this won't be pursued further.

4.3.13 The Posterior Cingulate (BA 30)

The identification in the linear trend analysis of a significant positive cluster in the left posterior cingulate (BA 30) in the control group (Table 3. 20) was problematic for interpretation as this area, as part of the DMN, would have been expected to correlate negatively with increasing cognitive load. However, inspection of the Talairach co-ordinates of the peak maxima (x = -29, y = -70, z = 13) indicated a position in the retrosplenial area, proximal to the optic radiations and Brodmann areas 17 and 18. This part of the posterior cingulate, posterior and inferior to the splenium of the corpus callosum, is also proximal numerous other fibre tracts. Cauda et al. (2010), who conducted a systematic and extensive mapping of connectivity of the posteromedial cortex (PMC) in the resting

state[56] affirmed correlations with a "task negative network" (equating to the DMN)[57.] However, their results also revealed a more nuanced pattern: A high degree of interconnectivity was observed within the PMC, although the posterior part correlated more with BA 30 than BA 23; however, BA 30, 31 and part of BA 23 were all "prevalently involved" with the DMN. This was not invariably the case as indicated below:

In our study, the retrosplenial cortex (BA 29 and BA 30) was characterized by selective functional correlations with the medial aspect of the temporal lobe and a number of subcortical structures, including the amygdala, the left nucleus accumbens, the left claustrum, and the caudate (left: positive correlation; right: negative correlation), and the dorsomedial thalamus (both positive and negative correlations). Again, these results replicate with fair accuracy the connectivity patterns observed in the primate brain. (Cauda et al., 2010, p.9).

Therefore, the increasing activation the left posterior cingulate cortex in a relatively small cluster (80 voxels) in the control group, could be explained by such variation in the connectivity of BA30 rather than being an anomalous observation. It might also have arisen in relation to the significant clusters exhibiting a positive linear trend in the left claustrum and left thalamus because of the correlations uncovered in their analysis.

4.3.14 Some correlations with the haemodynamic response

Correlational analyses were conducted between the haemodynamic response and positive and negative symptoms. These are reported in section 3.12. As strategies and performance may tend to diverge among participants with increasing cognitive load, the correlations are likely to vary and lessen accordingly.

Correlations between haemodynamic response and 0-Back SDs are discussed above in the section on the precuneus and wider posteromedial cortex (these are shown in Appendix 6). At first sight the unexpected observation of greater activation in the DMN nodes being associated with lower mean 0-Back SDs (suggestive of better attention) required explanation, however a reconciliation has been suggested by observations of increased activity in the DMN network while other areas are suppressed (section 4.3.10).

[56] Cauda et al., employed two different techniques which systematically explored the intrinsic connections of the posteromedial cortex with 10 "equispaced" regions of interest.

[57] The term was probably used instead of DMN as TTN activity anticorrelates with a "task positive network" (TPN) and is also discernible in spontaneous activations in the resting state.

Only one correlation was observed with positive symptoms, this indicated that greater suppression of the medial frontal gyrus in the 1-Back condition was associated with fewer positive symptoms. This might indicate that positive symptoms are more likely to interfere with suppression of network activity.

With respect to correlations with negative symptoms, a greater suppression of the medial frontal gyrus in the 2-Back condition and postcentral gyrus in the 3-Back was associated with a lower level of negative symptoms. Both areas are associated with the DMN. In addition, greater activation of the ACC and parahippocampal gyrus in the 3-Back condition was associated with fewer negative symptoms. The involvement of the latter possibly suggests the involvement of memory processes, while the engagement of ACC would be predicted to facilitate performance. Collectively, this suggests that better suppression of DMN areas is accompanied by greater activation in task positive networks, however, this may be weaker in the presence of a higher level of negative symptoms.

Finally, significant correlations were observed in the core nodes of the salience network were observed in relation to estimated FIQ (Tables Appx. 6.5, 6.6).

4.3.15 A General Conclusion

It is tentatively proposed, the implication of highly metabolically active hubs may be suggestive of a general impairment affecting large scale networks. Further, the negative correlation in verbal and visual learning with increasing time to access a trial of clozapine from the point of diagnosis, could be compatible with progressive deficits in synaptic plasticity as proposed by Friston et al., (2016) and Stephan et al. (2009). Further, this might be consistent with a glutamatergic hypothesis/ cortical disinhibition model in the characterisation of TRS (summary model at 5.1).

4.4 Some Limitations

Possibly the chief limitation of this study is the lack of a FLRS group for comparison with the TRS group. However, given the heterogeneity of schizophrenia it may have been difficult to ensure they were appropriately matched. In addition to age and gender, for example, it may have been helpful to match them on a primary characteristic like processing speed or estimated IQ. The reason for the absence of inclusion of a clinical comparison group e.g. schizophrenia patients responding to first line antipsychotics, was a limited availability of funds to perform fMRI. The absence of such a group represents a main limitation of the study, as our results were unable to account for clinical status and thus to address the question whether TRS might represent a distinctive aetiopathological subgroup of schizophrenia or is simply a more severe form of the disorder. What the study was able to investigate, however, were cognitive and neuroanatomical differences between the TRS symptomatology groups, highlighting haemodynamic changes associated with potentially therapeutic effects (and with lack of treatment response).

A larger sample would have also been desirable, particularly in view of the presence of participants with marked asymmetries between the WASI subscales. Also, there may have been a wider range of psychopathology. In the light of difficulties in recruitment, it is not possible to infer, for example, how exceptional the individuals with distinctive profiles in the VIQ>PIQ subgroup were, or indeed whether the proportion of the group with an asymmetry favouring PIQ (PIQ>VIQ) would have increased had there been a higher prevalence of negative symptoms. A larger sample may have also been helpful for comparisons between the lower and higher PANSS groups since these may have been under-powered; similarly, between male and female participants (an aspect which was not investigated for this study).

Similarly, a larger number of participants would have augmented the neuropsychological and behavioural measures, where corrections for multiple comparisons were not applied even though the Bonferroni statistic was usually supplied. To do so, would have been against the exploratory nature of the study in a rarely studied population. Instead, exact p-values were cited and effect sizes were considered during interpretation. However, it seems quite possible (in the light of normal to good estimated IQ scores), a more homogeneous and higher "functioning" group may have been recruited than would have been otherwise the case without the difficulties in recruitment.

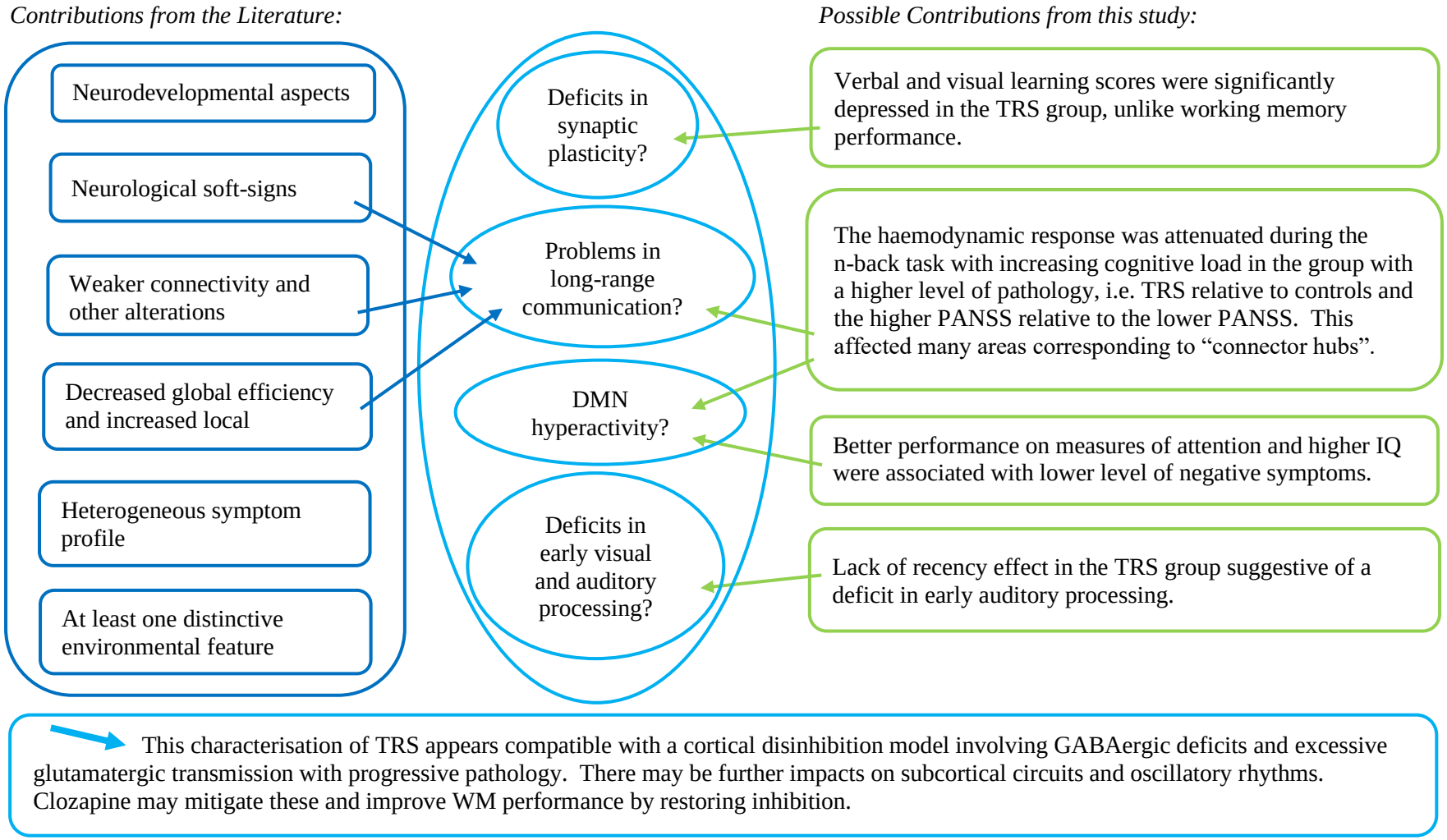
It may have better to have a slightly longer version of n-back, but scanner time was limited. Nonetheless, it was remarkable that the proposed proxy variable of sustained attention based on average SDs in the 0-Back condition was so robust when this was based on just 9 responses per participant. Also, a shorter duration minimised the risk of fatigue arising during the task. (Trial by trial analysis of the data raises this possibility as accuracy decreased in the TRS group, relative to the control group, on the last two trials: Figure 3. 9).

As proposed in this thesis, hyperglycaemia is a very common side-effect of treatment with clozapine so developing insulin resistance could provide an explanation for the attenuated changes in the haemodynamic response in this study; it would have been good to control for this by administering the oral glucose tolerance test since this is a more sensitive measure than tests of free glucose, hip-waist measurements or the body mass index.

A further possible limitation is that errors were not modelled in the analysis in the interests of conserving data, nor were d'prime values used. Fortunately, the error rates were very low in the control group and in the TRS group with most errors occurring on the second trial of the 3-Back condition, which is interpreted as indicating participants were trying to perform the 3-Back although their strategy was less successful at that point.

CHAPTER V

5.1 A Summary Model Characterising TRS based on the Literature and Results of this Study



5.1.1 Notes on the Characterisation of TRS in the Summary Model

Figure 5. 1 shows a summary model that characterises TRS and includes contributions from the literature on the left-hand side, proposed features relating to the aetiopathology of TRS in the middle and possible contributions from the current study on the right-hand side.

- Contributions from the literature

The published literature suggests that TRS may represent a distinct aetiopathological subgroup of schizophrenia comprising around 21% of all PSZ and is characterised by several biological features. (As such the group may represent a potential confound in some studies). Some of these may indicate a neurodevelopmental basis including an earlier age of onset and a lack of sex difference in prevalence (Wimberley et al., 2016). It is proposed the latter might reflect an onset before possible protection or benefit afforded by mature levels of female sex hormones. Compatible with an earlier onset, TRS is present at the first episode of psychosis in 70-84% (Lally et al., 2016; Demjaha et al., 2017). TRS individuals also exhibit normal synthetic capacity of striatal presynaptic dopamine in contrast to FLRS (Demjaha et al., 2012; Kim et al., 2017). However, elevations in glutamate/glutamine in the ACC have been observed in individuals unresponsive to initial antipsychotic treatment (Egerton et al., 2012); and TRS not on clozapine (Mouchlianitis et al., 2016, a) which might lead to damaging pathophysiological processes as well as cognitive dysfunction.

Various lines of evidence suggest TRS may be characterised by deficits in long-range communication, for example, it is associated with more neurological soft-signs (de Bartolomeis et al., 2018). Also, weaker connectivity relative to controls between the frontal lobe and primary auditory cortex, the frontal lobe and cuneus, between the paracentral lobule and the occipital lobe (Ganella et al., 2017). Some connections were weaker in TRS participants relative to controls and stronger in unaffected siblings so potentially compensatory (Wang et al. 2015). Decreased global efficiency and increased local efficiency were observed in TRS and UFMs relative to healthy controls which were significant in cerebellar and visual modules (Ganella et al., 2018). It is suggested here, this might reflect an efficient trade-off which maximises resources if global connectivity has been compromised (Bullmore and Sporns, 2012).

One environmental feature associated with TRS which contrasted with FLRS individuals, was a higher incidence of living in provincial or rural environments at the time of initial diagnosis (Wimberley et al., 2016).

- Potential contributions from this study

Results in the current study show some support for the proposed mechanisms that have been discussed in the published literature, and these will be briefly discussed below:

The TRS participants who took part in this study had a group median estimated IQ at the 61st percentile norm, while working memory performance (verbal and visual) and category fluency appeared depressed in relation to this but were relatively intact compared to standardised norms. (Category fluency is associated with executive function as well as processing speed, for example, Shao et al., 2014). By contrast, verbal and visual learning scores were significantly below those for category fluency. Moreover, partial correlations with age as a covariate indicated verbal and visual learning may deteriorate with delays in accessing clozapine. These latter observations are suggestive of deficits in synaptic plasticity and progressive deterioration during periods of acute psychosis.

In the fMRI study, the haemodynamic response was attenuated during the n-back task with increasing cognitive load in the group with a higher level of pathology, i.e. TRS relative to controls and the higher PANSS group relative to the lower PANSS. This was reminiscent of the attenuation observed in selected areas following the administration of the NMDAR antagonist ketamine to healthy volunteers (Anticevic et al., 2012). In this study, the attenuation involved many areas - all of which might correspond to "connector hubs". These enhance long-range communication and minimise "wiring costs" (Fornito et al., 2011; Bullmore and Sporns, 2012). This converges with other evidence indicating impaired global connectivity; however alternative explanations should be considered, particularly the possibility of developing insulin resistance as side-effect of clozapine.

As so many hubs were implicated, it is perhaps unsurprising there was evidence of hyperactivity related to major nodes of the DMN (reflected in attenuated "deactivations"). Further support might be found in the intercorrelations between responding variability (0-Back SDs), the measure of sustained attention (CPT-IP), estimated FIQ and negative symptoms. The latter might be expected to be a feature of DMN hyperactivity which might also cause microlapses in attention affecting cognitive performance.

Finally, two incidental observations arose during testing which might point to deficits in early sensory processing. One was that the CPT-IP test appeared poorly tolerated by some participants even though it had been standardised with a PSZ population. Moreover, there was no recency effect on the first trial of verbal free recall (HVLT-R) with the auditory

presentation of a supra-span list. This could be an artefact of list construction as other detailed studies with PSZ have not observed this.

- Interpreting current evidence within a broader model based on cortical disinhibition

Specific observations in this study when set within the wider context of schizophrenia research may be compatible with a cortical disinhibition model where there is excessive glutamatergic activity which clozapine appears to prevent or ameliorate. There are several ways in which disinhibition might arise, for example, hypofunction of NMDA receptors on GABAergic interneurons (Olney et al. 1995, 1999), or perhaps at GABA-A receptors where PV^+ interneurons synapse with cortical pyramidal neurons (Grace, 2016; Marx et al., 2011; 2014), or reduced numbers of GABAergic interneurons in the ACC (Benes et al., 1991). An NMDA receptor antagonist might model any of these because the circuitry is inter-related. In view of the learning deficits observed in this study, it is also interesting to note that healthy male volunteers exhibited dose-dependent deficits in verbal learning following the administration of ketamine in Newcomer et al. (1999).

Evidence from the literature also supports "windows of vulnerability" across the lifespan (Keshavan, 1999). For example: early influences on the immune and endocrine systems; the vulnerability of interneurons which are the last to migrate (Grace, 2016). Adolescence provides another window (Monaco et al., 2015; Selemon et al., 2013). Neurodegenerative processes could also arise, for example, oligodendrocytes appear to be particularly vulnerable to glutamate excitotoxicity (Matute et al., 2006). It is further pondered whether thinly myelinated areas within association cortices might be at increased risk[58]. However, the transition to psychosis may not be inevitable but precipitated by a "hit", probably environmental (Abi-Dargham, 2017), which overwhelms protection and repair.

A cortical disinhibition theory would be consistent with observations of increased activity in the ACC in TRS individuals not medicated with clozapine (Mouchlianitis et al. 2016 (a); also, Egerton et al. 2012, as above). Further, it might be compatible with the evidence of the prospective SPECT studies of Molina Rodriguez et al., (1997, 1998) where responders to clozapine exhibited higher levels of perfusion when on conventional antipsychotics than non-responders: in the thalamus, basal ganglia bilaterally, left inferior DLPFC and in the

[58] "The regions with high areal expansion tend to be lightly myelinated, including prefrontal, inferior parietal, lateral temporal, and anterior cingulate cortices." (Glasser et al., 2010, p.1162). While Flechsig (1901) determined that the inferior parietal lobule is one of the last areas to complete myelination (Catani and Thiebaut de Schotten, 2012, p.241).

right superior DLPFC. Further, all these values were significantly higher than those in a normative database, as was the value for the left superior DLPFC for responders. Following treatment with clozapine significant reductions were observed in responders in the thalamus, basal ganglia and superior DLPFC. Similarly, a [^{18}F] Fluoro-deoxy-glucose PET study by Molina et al. (2005), reported reduced metabolism in the basal ganglia and PFC in TRS participants after 6 months of treatment with clozapine. However, interestingly, metabolism in primary visual cortex increased and was associated with an improvement in positive symptoms. Molina et al. (2005) proposed this might be related to thalamic dysfunction and its excitatory projections to the occipital cortex. It is suggested here, an increase in metabolism might reflect improved function following increased inhibition. Concentrations of GABA are higher in the occipital cortex than more anterior areas in healthy individuals (Hoftman et al. 2018) and so may play a prominent role in early visual processing, for example, mediating orientation-specific surround inhibition (Yoon et al., 2010).

An alternative model of cortical disinhibition has been proposed by Hoftman et al. (2017), who suggested a homeostatic downregulation of GABAergic activity in response to a decrease in glutamatergic transmission. As with the pathophysiological effects of increased glutamatergic activity, it was proposed GABAergic downregulation might lead to the collapse of the ability to generate oscillatory rhythms which support working memory.

5.2 Ideas for further research

This exploratory study, with a relatively small number of participants, has generated numerous ideas. They are not ranked according to importance, as this varies according to how they are evaluated, for example, from an academic perspective, pressing need or practicality. Given the lack of studies comparing TRS and FLRS in the literature, it may be useful to revisit several areas of previous exploration in schizophrenia research - this time, honouring this distinction and using the consensus definition of TRS as proposed by Howes et al. (2017), in which case, the list may be extensive, but the suggestions made here will take as their starting point observations arising within this study.

5.2.1 Insulin Resistance as an alternative explanation for the attenuated fMRI BOLD signal

An alternative interpretation is offered for the attenuation in the haemodynamic response in TRS and higher PANSS participants during the n-back as the involvement of highly active "hubs", might indicate metabolic failures and stress with associated weakening in functional

connectivity, even myelin deficits. As proposed above, this could involve developing insulin resistance related to the high metabolic liability of clozapine itself (Ahmed et al., 2008) and also be consistent with a recent review by Cha et al. (2015) of studies which have pointed to associations between relative hyperactivity in the DMN and metabolic disorders. It is proposed in this thesis (section 4.3.3) insulin resistance might compromise energy at highly active hubs. It has also been associated with white matter abnormalities in type 2 diabetes (T2DM), for example, in a study of 46 individuals with T2DM, Yau, et al. (2014) found extensive abnormalities indicated by increases in medial diffusivity (MD): ten were in the temporal lobe, including bilateral changes in the auditory cortex of Heschl's gyrus, the fusiform gyrus, the hippocampal areas and arcuate fasciculus), further MD increases were observed in the right insula, in the occipital cortex bilaterally (particularly around the calcarine sulcus), also in the frontal and parietal cortices. In addition, reductions in white matter integrity were observed: in the temporal lobe (including the arcuate fasciculus bilaterally, the left superior temporal and right middle temporal gyri), while the largest cluster of reduction was in the parietal lobe. The widespread nature of these changes associated with T2DM bears some similarity with the deficits in grey matter in TRS observed by Anderson et al. (2015, a), and, perhaps, also with the many areas of differential alterations in the haemodynamic response in this study, for example, an attenuation of the haemodynamic response was observed in the left parahippocampal gyrus (Figure 3. 25).

Metabolic aspects, e.g. hip-waist ratios, might have been informative in this study as they are a marker of metabolic syndrome. However, the oral glucose tolerance test would be more sensitive: evidence from the longitudinal Hisayama study of elderly Japanese observed an association between the development of mild cognitive impairment and the failure of insulin levels to normalise within 2 hours of glucose challenge. Whereas blood glucose levels were not a useful predictor (Ohara et al., 2011). Also, consideration should be paid to the diurnal rhythm, for example, it might be better to consistently measure insulin resistance and conduct neuroimaging studies in the morning, or at least a similar time of day.

5.2.2 Reductions in Global Efficiency – a biomarker of TRS?

The implication of widespread attenuations in the haemodynamic response at connector hubs in this n-back study could be consistent with observations on resting state functional connectivity by Ganella et al. (2017), who observed widespread reductions in the strength of functional connections in TRS individuals relative to healthy controls affecting 3.4% of the connections identified using their methodology. It was further inferred that the disorder might be characterised a disorder of "hub to hub" connectivity because of reductions in

global connectivity. Certainly, a failure to integrate information across different brain areas might help to explain some symptoms and is consistent with the implication of connector hubs in this study.

Since the observation of reduced global connectivity and increased local efficiency might provide a useful biomarker of TRS, particularly in the early stages (before further progression of pathology in FLRS), it is quite possible, a study has been recently been completed or is currently under way comparing FLRS individuals with TRS individuals who have been recently diagnosed. Better still, a prospective study before a trial of clozapine is tried, since clozapine may help to improve global network connectivity and potentially reduce differences with FLRS individuals who have also been acutely unwell. There may also be confounds in relation to delays in accessing clozapine, particularly from time of the first episode However, reductions in global efficiency with corresponding increases in local efficiency were also observed in unaffected siblings by Ganella et al. (2018), which may indicate this is an endophenotype of TRS, consistent with proposed trade-offs between local and global efficiency to optimise metabolic costs (Bullmore and Sporns, 2012).

If this pattern is distinctive to TRS (and first-degree relatives) and as seems likely, is present in the early stages, it may be possible to identify individuals at risk of TRS before they become unwell and perhaps treat proactively, if for example, elevations in immune, endocrine or other markers suggest possible transition to psychosis is imminent. Progress has been made by Sabine Bahn and colleagues using proteomic and metabolomic markers in relation to PSZ (referenced under Diagnostic Profiling below). However, the simple hypothesis in the first instances could be that at time of diagnosis TRS individuals will exhibit reductions in global efficiency and increases in local efficiency relative to healthy control and FLRS individuals, because TRS can be characterised as a disorder of impaired global connectivity.

5.2.3 A case register study of outcomes and speed in accessing Clozapine

To determine if delays in accessing clozapine from the point of a first admission or diagnosis might be associated with worse outcomes. These might be indicated by the number of hospital admissions and days in hospital. Also, whether greater benefit accrues with longer periods of treatment with clozapine (although the results of this study would indicate benefits may be achieved fairly quickly, i.e. possibly within the first two years).

5.2.4 A comparison of recency effect in TRS and FLRS groups in supra-span lists, with further tests of auditory acuity for verbal and nonverbal stimuli (and corresponding tests in the visual domain e.g. with backward masking)

The meta-analysis of 19 studies involving 1188 individuals at clinical high risk of psychosis by Fusar-Poli et al., 2012 (section 1.5.1) observed the greatest decrements in performance on tests of short-term verbal and visual memory, in addition to lower scores of general intelligence and cognition. Therefore, both TRS and FLRS individuals might show this. However, the decrement might be greater in TRS individuals and this study indicates further deterioration may arise during the period from diagnosis until treatment with clozapine which might reverse or interrupt decline.

An unusual and potentially important observation, which may be related to this and which will need replication was the apparent lack of recency effect in free recall on the first trial of the Hopkins Verbal Learning Test. However, the list began with the word 'lion' which is acquired early in a child's lexicon so it is proposed this may have evoked a powerful representation which might have distracted attention away from the items in the recency portion. Therefore, careful consideration should be given to the construction of word lists concerning factors such as age of acquisition, frequency, ease of articulation, concreteness, salience, list position and other factors which might affect recall. If replicated this would suggest a selective deficit of the phonological store which could contribute to impairment in the free recall of auditorily presented words (Vallar, 2006). As discussed in section 4.2.9, this might be predicted on the basis of preclinical studies which have highlighted potential vulnerability of the inferior parietal cortex/posterior cingulate to glutamatergic excitotoxity consequent to the operation of disease or, perhaps, NMDAR antagonism with ketamine or PCP (Olney et al., 1999). Importantly, not only might this provide an index of illness severity, but a deficit in recency might provide a specific biomarker of TRS.

Related to this (on the basis of neuropsychological observations on acquired damage (Warrington et al., 1971) degenerative changes might be localised to deformations of the posteromedial surface observable in sMRI data or abnormal connectivity in aspects of the superior longitudinal fasciculus which includes the arcuate fasciculus and has terminal projections in the PFC. The corpus callosum might also be affected posteriorly. A relationship might be found between aspects of recall and perceptual tests of auditory acuity for verbal and nonverbal stimuli (as in Bruder et al., 2004 – although, their word lists were too short to show a deficit in recency). Also see 5.2.6 below.

Perceptual problems can arise for a variety of reasons, for example, “glue ear” during early childhood, but in schizophrenia these might arise from a lack of specificity in the signal at the encoding stage which might be related to deficits in selective attention (Engle et al., 1999; Gandal et al., 2012, figure 3). The introduction indicated ways these might arise, for example, a lack of inhibition arising from low GABA in the visual cortex, or perhaps dopamine dysregulation in the prefrontal cortex at a later stage of processing, or difficulties in integrating information in the striatal-thalamo-cortical loops. (Also, various neuromodulators could give rise to imbalances at different stages).

It is further predicted that TRS individuals might be more likely to have perceptual deficits than FLRS individuals. Also, their short-term learning deficits are more likely to be related to a glutamatergic aetiology, whereas FLRS may be more likely to have deficits in learning and verbal working memory related to dopamine dysregulation in the prefrontal cortex. On the basis of the evidence in this study with TRS individuals, negative symptoms might be more likely to be associated with perceptual and sensory gating deficits than higher cognition, although it is possible, clinical symptoms across the group were insufficient to show the latter. Finally, it would be interesting to see if unaffected first-degree relatives have perceptual deficits and exhibit an attenuated recency effect in the free recall of auditory-verbal lists. This could indicate encoding problems may be related to perception rather than arising during the course of the disease. It is an empirical question whether there might be corresponding deficits in the visual domain mediated by similar factors.

5.2.5 A study of intellectual asymmetry in unaffected first-degree relatives of TRS and FLRS individuals

It is apparent the WASI subscales may be prone to asymmetry, yet intellectual asymmetry has been observed in PSZ with other measures. A simple search of the PubMed data base using the terms “IQ OR “intellectual” AND asymmetry AND schizophrenia” conducted 31.7.19 yielded only 18 results. Many of these concerned differences in the lateralisation of fibre tracts, which could provide a related line of enquiry.

It might be helpful to repeat the design of Kravariti et al. (2006), who observed intellectual superiority in the VIQ scale over the PIQ in unaffected first-degree relatives of schizophrenia. A short version of the Wechsler Adult Intelligence Scale - Revised (WAIS-R, Wechsler, 1981) was administered which may be less prone to variations in scores between the subscales than the WASI (section 4.2.7). Its purpose would be to assess and compare intellectual asymmetry between the first-degree relatives of individuals with TRS

and FLRS to ascertain whether these might reflect contrasting endophenotypes for schizophrenia. This has several advantages, not least because it may be easier to recruit participants who have not endured a major mental illness or taken psychotropic medication. This would also permit the examination potential sex differences where pre-menopausal women might be afforded some protection against glutamate excitotoxicity by ovarian hormones. A further hypothesis is that that a more distributed organisation of fibre tracts, as might be associated with fluid intelligence could offer some protection against excitotoxic and oxidative events in local circuits.

Certainly, genetic factors could underlie asymmetries in performance, for example, in a study of healthy twins by Budisavljevic et al. (2016), a significant and asymmetric familial effect in the volume of the dorsomedial cingulum was observed that accounted for 51% of the variance in the left hemisphere while in the right hemisphere this contribution at 34% was nonsignificant. However, other tractography measures (medial diffusivity and fractional anisotropy) indicated major genetic effects in both hemispheres. They further observed FA of the cingulum has been observed to be positively correlated with FIQ and PIQ (Chiang et al., 2009). This was also consistent with Luders et al. (2007) who found the volume of the isthmus of the corpus callosum correlated positively with IQ and that FIQ and PIQ had the largest effect sizes.

5.2.6 A comparison of TRS and FLRS participants on sensory gating

Worse performance on memory tests have been associated with decrements in auditory perception (e.g. Bruder et al, 2004), or when artificially caused through manipulations such as the word length effect or acoustic similarity effect. It might be predicted TRS may be unaffected by phonological similarities between words (Conrad, 1964), or word length (Baddeley, Thomson and Buchanan, 1975) since they may already have poor phoneme discrimination. Such deficits could be related to sensory gating deficits and also contribute to deficits in short-term verbal and visual learning on the basis of a worse signal to noise ratio, and/or because encoding requires more processing capacity to make representations more distinctive.

Even though clozapine appears to have some efficacy with sensory gating (Micoulaud-Franchi et al. 2015). One clue to the possibility of greater sensory gating deficits may have come from the observation that the CPT-IP was poorly tolerated in some participants in this study, indicating possibility that the test stressed selective attention when perceptual capacities were under strain. This would be more likely to occur with longer letter stimuli

where different letter representations in memory may compete for identification (McClelland and Rumelhart, 1981). A more rapid rate of presentation (one item per second) with infrequent breaks could also make it harder to recover between trials. In a recent multicentre study of schizophrenia using a visually degraded form of the CPT (DS-CPT), worse performance was observed in individuals with a higher level of symptoms, however, this was statistically inconclusive because of insufficient numbers of participants with higher PANSS at some centres; also, this kind of study is vulnerable to poor inter-rater reliability (Nuechterlein et al., 2015). It should also be calibrated to avoid floor and ceiling effects. An easier approach might be to compare TRS and FLRS participants on a perceptual task involving backward masking to see how much time participants require to process the information (consciously and pre-consciously).

5.2.7 Further explorations of myelin deficits in TRS and FLRS including areas corresponding to the distribution of Von Economo Neurons

Following the proposal by Smucny et al. (2017) that VENs could be compromised, it might be worthwhile to follow the example of Cauda et al. (2013) and apply a mask to a DTI dataset comparing TRS, FLRS and HC to see if white matter decrements are concentrated in areas where VENs have been found (e.g. ACC, DLPFC and anterior insula) in an attempt to rule out a selective deficits. VENs enable rapid communication at distance and a deficit would be consistent with the implication of the connector hubs in this study. It might also help to explain the low scores on social cognition as VENs have been proposed to support this (Butti et al., 2013); or indeed any task that requires the rapid processing of information across large-scale networks. Moreover, a deficit in VENs could also increase demands upon connector hubs and increase the likelihood of damage.

From a TRS perspective, regions of interest may include thinly myelinated areas which may be particularly vulnerable to various form for damage (excitotoxic, oxidative, redox). These include the prefrontal, insular, cingulate, temporal and parietal association cortices. In the interesting study by Vanes et al., 2018, no differences were observed between TRS and PSZ groups with respect to myelin abnormalities, however, it is suggested that any difference in thinly myelinated areas could be relatively small and perhaps the signal might be obscured by the presence of more thickly myelinated layers, described in Glasser et al., 2011.

5.2.8 Histology studies in TRS and FLRS concerning the density of VENs and GABAergic interneurons

While Benes et al. (1991), provided a seminal observation concerning depletions in GABAergic interneurons these are so numerous decrements may be difficult to quantify but it might be predicted there are deficits in PV^+ GABAergic interneurons relative to control samples and these could be greater in TRS than FLRS. By contrast, VENs are less numerous, rare in evolution and may still to be reported in some areas of the human brain. However, they are large, myelinated and have a distinctive spindle or corkscrew shape with an absence of collaterals along the main length and so might be easier to quantify. Again, they might be less numerous or smaller in TRS than FLRS and healthy controls, perhaps especially in the ACC where chronic hyperactivity (Mouchlianitis et al., 2016, a) might have resulted in sustained myelin damage, neuronal atrophy or loss.

5.2.9 The Claustrum in TRS and FLRS

Another ROI which may reward study is the claustrum where significant differences were observed in the haemodynamic response between the lower and higher PANSS groups in this study. This has the potential to provide compensatory support to the salience network and selective attention through its widespread connectivity, however, it might also be vulnerable to widespread deficits in myelin and related deficits in connectivity. Either way individuals with a higher level of symptoms might be predicted to have smaller grey matter claustral volumes than those with a lower level of symptoms. However, a comparison with matched healthy controls might help to indicate whether differences in the claustrum might be compensatory or due to pathophysiological processes. Given the topographical organisation of the fibres, any changes might be predicted to affect the anterior claustrum. Further, this may be a point of difference between TRS and FLRS participants although perhaps this is less likely after Vanes et al. (2018).

5.2.10 fMRI BOLD Studies

It is expected the literature will continue to expand and further support may be found for the idea that one source of attention deficit may arise from DMN dominance (hyperactivity of some areas). This may not be a feature that is unique to TRS, for example, Fryer et al. (2013) made similar observations in their study of individuals at high risk of psychosis or with early psychosis. Hyperactivity was also observed in the medial prefrontal cortex during the encoding phase of a working memory task in unaffected siblings of PSZ (de Leeuw et al., 2013). However, as suggested above, hyperglycaemia/insulin resistance may

possibly cause this kind of dysfunction (for example, see Cha et al., 2015). Indeed, as this was not controlled in this study, it is possible the observations might be attributed to this rather than pathology directly related to TRS. Therefore, it could be informative if a future BOLD fMRI study controls for this.

It would also be advantageous to include a group of carefully matched FLRS participants in a future study. Another lesson learned concerning participant selection - from this study and research using molecular neuroimaging (e.g. Goldstein et al., 2015 vs, Mouchlianitis et al., 2016, a) is that clozapine treatment may "normalise" observable function in some individuals, so medication is an important consideration. I also agree with So et al. (2018) that group homogeneity may be important, as significant differences in this study appeared to depend on increasing cognitive load to a high level. It is therefore important participants are able to perform the task across all levels and helpful to ascertain when performance starts to degrade whether this is for similar reasons, or if there is a divergence in strategy. So et al. (2018) suggested group homogeneity was improved by a screening process which resulted in the selection of a "high-performing" schizophrenia participants (something that may have been inadvertently achieved in the demanding nature of this study).

5.2.11 sMRI investigations of the Hippocampus, ACC, Insula and Posteromedial Cortices

The structural data has been collected and could be correlated with neuropsychological variables. While the hippocampus has been extensively studied and schizophrenia research, it would be remiss not to look at the hippocampal volumes in TRS, given its importance to memory function and because the hippocampus has been proposed as, possibly, the primary site of pathology in schizophrenia (e.g. Grace, 2012, 2017). Many lines of evidence implicate stress in the genesis of schizophrenia and the hippocampus, which a site of feedback for glucocorticoids as it is involved in regulating the HPA axis, and particularly vulnerable to an excess (Mondelli et al., 2010), perhaps especially in the context of another pathology that compromises energy (e.g. Armanini et al., 1990; Herbert et al., 2006; Jacobson and Sapolsky, 1991). It therefore seems highly likely hippocampal volumes will also be reduced in TRS (although there may be regional variations). Attempts have been made in this thesis to consider alternative loci for primary pathology in TRS, however, all roads of enquiry may lead back to the hippocampus as it has a population of fast-spiking parvalbumin positive interneurons (e.g. Zaletel et al., 2016), which are vulnerable to chronic stress and quite possibly other insults. The vulnerability of PVIs to damage and their important role in putting inhibition onto excitatory networks is elaborated upon by Grace

2016, whose argument was not specifically directed towards TRS but which might apply very well (also relevant, section 1.5.5).

5.2.12 Investigations of Oscillatory Rhythms

Emerging evidence suggests neural synchrony is important for the integration of information across large scale distributed networks (e.g. Uhlhass and Singer 2006, 2008; Sirota et al., 2008) and several studies have observed weaker long-range gamma phase synchrony during working memory tasks in schizophrenia (e.g. Chen et al., 2014; So et al., 2018; Haenschel et al., 2009). Given the conclusion of this research is that TRS could be well-characterised by deficits in long-range communication (possibly distinguishing it from FLRS), electrophysiological methods might be particularly suited to the study of TRS and might be used with other approaches. However, it is also possible to measure the amplitude of low-frequency fluctuations (ALFF) in the rsfMRI BOLD signal as demonstrated by Fryer et al. (2015) who observed an association between a neuropsychological measure of sustained attention and reduced ALFF values in the bilateral posterior parietal areas, posterior and dorsal anterior cingulate and right DLPFC in participants with schizophrenia relative to controls (n=168 and n=166 respectively).

5.2.13 Historic Drug Use

While recent evidence suggests TRS is present in the majority from the first episode of psychosis, it now generally accepted there may be many paths to psychosis (Murray, 2017) and even though TRS has been generally disregarded as a separate category, it is quite possible this may also be true of TRS. Premorbid drug abuse might be one vulnerability factor and it is estimated (Appendix 1) that 72% of the TRS participants may have tried drugs which increase striatal dopamine. The majority had tried drugs with serotonergic effects or had serotonergic and dopaminergic effects combined. Current illicit drug taking was not considered in this study and drug screening tests are rare except for molecular imaging studies, however, concurrent use appears common if widely under-reported (Bahorik et al., 2014,b).

The diversity of drugs available today and polydrug use pose a problem for surveys which might seek associations between exposures to particular kinds of drug and mental illness. However, the participants in this study were from a generation who had access to a more restricted choice. There are concerns about data which relies upon subjective recall, particularly in participants who may have cognitive deficits; however, it is suggested “first

ever" experiences might be better retained on the basis of their novelty and also the "primacy effect" (Baddeley, 1986). Also, while a considerable mismatch between self-report and the drug-screening results was observed in a study of more than 1000 individuals (Bahorik et al., 2014,b), individuals may be more willing to share "historic" information.

The potential value of research into possible pharmacological antecedents of FLRS and TRS partly arises from concern that psychedelics are being commonly used. An interesting case is also building for their use in therapy, possibly in relation to anxiety, depression and OCD (Carhart-Harris, 2016; Pollan, 2018), but the hazards are far from understood. The responses to few demographic questions and cross-tabulation with the date of diagnosis demonstrated this might be feasible and recruitment for the purpose of a short interview should be far easier than for a neuroimaging study.

5.2.14 Adjunctive Treatments in TRS

These suggestions are based on the alternative explanations for the widespread attenuations in the haemodynamic response observed in this study.

- Metformin

With respect to the hypothesis, this might be related to transient deficits in energy metabolism, it is proposed that the early use metformin to improve insulin uptake might be particularly helpful in TRS. Not least, in helping guard against developing insulin resistance given the high risk of hyperglycaemia associated with clozapine treatment. The use of metformin as an adjunct to clozapine has already shown promise (Hebrani et al., 2015; Wu et al., 2008).

It is the development of occult insulin resistance, as well as diabetes which are both linked with neurodegeneration that is particularly concerning (Ohara et al., 2011, Chen et al., 2016) in the light of clozapine's adverse profile for metabolic side effects. As mentioned in section 1.5.8, there is some limited evidence that suggests glucose dysregulation may be a premorbid feature (Guest et al., 2011), with a heighted prevalence in first-degree relatives (e.g. Thakore et al., 2002; Henderson, et al., 2005)[59]. Identifying the prevalence of this

[59] In an interesting convergence, insulin in the hippocampus may have a role in promoting the expression of extra-synaptic GABA A receptors by trafficking them to the cell surface. This affects membrane properties such as the resting membrane potential and firing patterns and was demonstrated to decrease the excitability of neurons in layers 5-6 of the prefrontal cortex (Trujeque-Ramos et al., 2018).

potential problem would be a valuable step and not a counsel of despair (clozapine remains the "gold standard" and perhaps only effective treatment of TRS) because, as above, there is evidence that adjunctive treatment with metformin may lead to weight loss and improve insulin sensitivity. Insulin resistance is widely underdiagnosed or not controlled properly in the general population and, excess body fat which is often associated with this is itself a source of inflammatory cytokines. Given observations of a generally higher rate of morbidity from all causes in schizophrenia, considerable benefit might be gained by controlling insulin resistance which affects so many systems.

Similarly, to minimise challenges to energy metabolism thyroid function should be carefully evaluated by checking free thyroxine and not just thyroid stimulating hormone. Further improvements may be made by ensuring a good quality of sleep but without sedation during the day. It follows, good sleep habits and the timing, as well as the dose of clozapine may be important factors in optimising adherence and treatment.

- D-serine

If TRS is well characterised by a glutamatergic hypothesis, then the use of an adjunctive that facilitates transmission at the NMDA receptor might be beneficial. However, it may have less benefit if clozapine already facilitates this (Farber et al., 1998; Tanahashi et al., 2012). The use of D-serine as an adjunctive has also shown some promise and, perhaps, might be used with all FEP cases to prevent excitotoxicity associated with NMDAR hypofunction?

- Modulation of Nicotinic Receptor Agonism as an Adjunctive Treatment?

Koukouli et al, 2017 have suggested a therapeutic role for nicotine in schizophrenia, for example, Shaqiri et al., 2016 observed nicotine helped to reverse deficits in visual backward masking which increase with age and also in first-degree relatives of individuals with schizophrenia. In a study of performance on the CPT-IP and a degraded stimulus version of the CPT (DS-CPT) by 1140 participants with schizophrenia, Nuechterlein et al. (2015) observed that current and past smoking were associated with slower responses to targets, and current smoking was also associated with worse accuracy. Perhaps, those participants were more likely to smoke because they have greater need of stimulation? Ettinger et al., 2107, observed nicotine had general arousing effects in their healthy participants but may lack specific effects on selective attention. However, another study indicated nicotine may improve selective attention in PSZ, also nicotine improved working memory in the PSZ group while worsening that in the control. (Jacobsen et al, 2004). Consequently, it is

observed individual differences and also nicotine dependency may be important variables. Moreover, in explaining contrasting observations on connectivity between executive networks and the ACC, where it was reduced in the control group and increased in the PSZ group, Smucny et al., (2017) observed this could reflect an inverted-U function whereby sensitivity to agonism at nicotine receptors may be enhanced in individuals who have relatively low levels of receptors, whereas, signalling might become sensitised in healthy individuals who had normal levels before nicotine administration. In a preclinical study, clozapine was observed to induce acetylcholine release in the rodent PFC, striatum and nucleus accumbens without the development of tolerance (Parada et al., 1998).

As discussed in relation to the different prevalence of smoking in the lower and higher PANSS groups, a large body of evidence suggests nicotine may improve cognition in schizophrenia and help to ameliorate negative symptoms, which may make this of particular interest to TRS research (Patkar et al., 2002). Also, the anterior cingulate (including the dorsal cingulate cortex) and striatum are regions of interest in TRS research that are modulated by nicotine. Empirical work has been conducted in healthy and PSZ populations which indicates nicotine may affect the connectivity of networks and particularly the salience network involved adaptive behaviours and switching across networks (Hong et al., 2009). Smucny et al., 2017, suggested nicotine or other stimulants could be used to improve connectivity in large scale networks. Nicotine may also help to decrease DMN activity when attention is oriented towards task positive activity (Tanabe et al. 2011). The cognitive effects of nicotine appear to involve "cholinergic projections to the neocortex, and hippocampus, influencing inter alia glutamatergic and GABAergic neurons" (Kumari et al., 2003, p.1002). It is therefore unsurprising that nicotine has been observed to improve attention, accuracy and working memory performance (Kumari et al., 2003).

When viewed from network perspective it seems possible that stimulants which increase processing speed, may also alter resting state connectivity (e.g. Jacobsen et al. (2004) and affect networks (e.g. Hong et al., 2009; Tanabe et al., 2011). Moran et al. (2018) reported nicotine increased activation in the right caudate following task errors in participants with schizophrenia compared with controls, while both activation in the dorsal and rostral ACC was increased in both groups. Behaviourally, nicotine appeared to improve adaptive performance in the schizophrenia group, providing further evidence of improved cognitive control and a shift in attention away from consuming default-mode activity towards more task positive activity. Tanabe et al., 2011 may have observed a similar change following the administration of a nicotine patch in a rsMRI study of healthy non-smoking individuals where DMN activity was attenuated while an increase in activity in extra-striate areas was

observed, which was interpreted as a shift from the DMN towards networks involved in the processing external information. Phenomenologically, such a shift might help to "keep the demons at bay"[60] in schizophrenia and help to explain the high prevalence of nicotine dependency. Better understanding of these aspects could inform therapy directed at emotional regulation and smoking cessation.

- Alternatives to Clozapine?

Where individuals are unwilling to try clozapine or it is not suitable for another reason, promising research indicates pregnenolone or one of its metabolites may be a useful treatment. As with clozapine, the reasons for potential efficacy are unclear but their actions may overlap (for example, if they both have modulatory actions at the same GABA-A receptor). This could make it less likely they would be more effective in combination; however, they could be useful as alternatives.

5.2.15 Immunological and Endocrine Investigations

Recently, there has been growing interest in associations between immune factors and schizophrenia, for example, with observations of vitamin D deficiency which affect the immune system (Lally et al., 2016); also, associations involving stress and childhood trauma (Mondelli et al., 2011). It has been observed in thesis that the persistence of certain negative symptoms bears some similarity with "sickness behaviour" in animals when they become unwell (section 1.10.4). This observation has been made by others and an immunological perspective has been advanced by Bullmore (2018). Given the persistence of negative symptoms is a feature of TRS and may already present at the first episode of illness, TRS individuals may be more likely to have increased levels of inflammatory markers than FLRS (at least before Clozapine treatment has started). Indeed, these might be a suitable biomarker for TRS when used in combination with other features (next section).

Further, TRS individuals and their UFMs may be more suitable candidates for immunological treatment compared with FLRS, because the persistence of negative symptoms is a feature of TRS. According to a review by Zhang and Zhou (2014), minocycline inhibits microglia activation and has been effective in treating negative symptoms in several trials and mitigates the effects of glutamate excitotoxicity (e.g. Monte et al., 2013). Also, higher levels of inflammatory cytokines in FEP individuals predicted less improvement in clinical symptoms (Mondelli et al., 2015). Further, inflammation may

[60] This was how a non-participant described the effects of smoking on their schizophrenia.

be localised as well as systemic, for example, there have been case reports of hyperperfusion in the posterior cingulate being reduced with a combination of minocycline and antipsychotic treatment (Miyaoka et al., 2007; Chavez et al., 2010). As one of the most metabolically active areas in the brain, the posterior cingulate may be suitable target for this therapy.

It was with considerable expectation a prospective RCT was conducted with minocycline as an adjunctive medication administered to FEP individuals for a year (Deakin et al., 2018; Lisiecka et al., 2015). Unfortunately, there were no significant differences between the placebo and minocycline group with respect to the outcome measures (grey matter volume in the mPFC and DLPFC activation in the n-back task) and it was concluded that the drug should not be administered unless there are signs of active inflammation. Yet it is possible, this course of treatment is more likely to be effective in TRS participants, in which case the trial would have lacked power to detect a significant effect. Also, it is suggested here the outcome measure used in the BeneMin study of grey matter volumes might be less suitable for use with TRS individuals in the light of a report by observations by Ahmed et al. (2015) that these may continue to decrease during the year after commencement of treatment with clozapine. As clinical improvement was seen during this period, it was observed progressive decrements in grey matter might not be pathological, for example, it might be consistent with the pruning of aberrant connections. Kishimoto et. al. (2018) observed it may be premature to terminate research on immunotherapy, while Deakin et al., (2018) acknowledged other subgroups might be suitable candidates.

Abnormal endocrine activity may also be linked with TRS: in a study by Mondelli et al. (2015), a blunted cortisol awakening response (CAR) was also predictive of a poor treatment response, possibly indicative of long-standing overactivity in the HPA, which may have implications for other systems (section 1.10.5). Consistent with this, larger pituitary volumes (reflecting, in part, greater activity in the corticotroph cells) have predicted a poor treatment response (Garner et al, 2009), and blunted CAR has been observed in individuals at ultra-high risk of developing psychosis (Day et al, 2014), while larger pituitary volumes have been observed in unaffected relatives, suggesting there may be a "genetic susceptibility to over-activate the HPA axis" (Mondelli et al., 2008, p.1004).

5.2.16 Diagnostic Profiling of TRS using Multiple Biomarkers

A combination of biomarkers which need not be from the same category could progress the identification and treatment of TRS. Mondelli et al. (2015), for example, recommended cytokines could provide a marker of treatment responsiveness. Pattern recognition techniques using artificial intelligence (for example, the support vector machine), can accommodate a diverse range of measures (at least to begin with, until their utility is determined). This approach, taken by Sabine Bahn's team, involving the molecular analyses of CSF, has shown considerable promise (e.g. Holmes et al., 2006; Huang et al., 2006; Huang et al., 2007; Guest et al., 2013; Schwarz et al., 2010), but this might prove even more useful if the distinction between TRS and FLRS is observed and a wider range of measures is incorporated. A search of the literature in molecular biology (encompassing genetics and neuroimaging) and preclinical studies can provide more e.g. a screening study by Malik (2011) indicated treatment with clozapine increases neurotropins such as BDNF, NGF, also TTR (thyroid hormone and retinol carrier which sequesters B-amyloid in the CSF). Clozapine was also observed to upregulate transthyretin (TTR) in the rat hippocampus after 4 weeks of treatment by Chen and Chen, 2007.

Subject to practical considerations, other biomarkers might include measures relating to CAR and other endocrine information relating to sex hormones and insulin resistance which, as previously suggested (5.2.10), might be an important factor to control considering the relative hypometabolism reflected in attenuated responses in this fMRI study. Also, because cognitive impairment may arise in association with hyperglycaemia and developing or occult insulin resistance. The posterior cingulate may be particularly vulnerable to hyperglycaemia and is one of the first areas to develop pathology in Alzheimer's disease (Buckner et al., 2005; Vlassenko et al., 2010). Genetic information, molecules in plasma, vitamin D, inflammatory cytokines, d-serine might also provide biomarkers, as might neuroimaging measures such as resting state connectivity and proton magnetic resonance spectroscopy (1H-MRS), for example to measure GABA. Also, white matter, for example, in a prospective study of 63 FEP participants, non-responders exhibited lower fractional anisotropy than responders and control participants, mostly in the cingulum and corpus callosum, also the uncinate. This improved in both responders and non-responders after 12 weeks of antipsychotic treatment (Reis Marques et al., 2014).

Some putative biomarkers suggested by this study include the possibility that TRS individuals might have worse sensory gating deficits and need more time to assimilate early perceptual information, so a backward masking technique could be used to explore this and

perhaps also drug responsiveness. Simple standard deviations might be obtained in the baseline task of a CPT-X paradigm (similar to the 'Is it X' condition of the n-back task) which might provide a measure of variability in responding and usefully index sustained attention. However, the main problem may lie not with cognitive control but with the ability to resist interference (i.e. selective attention), which Engle et al. (1999) described as "the critical factor common to measures of WM capacity and higher level cognitive tasks" (p.312) Indeed, it will be interesting to learn more about the relationship of GABA as well as dopamine as potential modulators of selective attention.

In the inexpensive category of ideas for further research, as already suggested above (section 5.2.4), the recency effect in TRS individuals may reward further investigation if it transpires it is abolished and is usually specific to TRS. Further, it might be useful to explore whether post-error slowing (which appeared to be abolished in the behavioural data for TRS participants), might form the basis of a test which indexes of ACC behavioural monitoring function. This might be expected to improve with treatment response. However, at the outset, it might be predicted that this function may be more compromised in TRS compared with FLRS.

Finally, in view of the increasing numbers of studies which are finding shared endophenotypic characteristics in unaffected first-degree relatives, it should perhaps be considered that, free from antipsychotic medication, they too might provide a source of useful biomarker information.

5.2.17 Proton magnetic resonance spectroscopy (1H-MRS)

Finally, it is important to revisit what has already been learned. An example of project that might fall within a "moonshot" category - where the evidence base that it might work is limited but the potential reward is great, may be offered through the advent of 1H-MRS which has clear advantages over studies which have had to rely upon analysis of CSF to explore certain questions. One potentially interesting biomarker of TRS (or rather the converse, FLRS) identified through CSF studies, concerns the elevation of homovanillic acid (HVA), a metabolite of dopamine (Pickar, 1992). This was subsequently replicated by Risch and Lewine (1993) and is compatible with a dopaminergic hypothesis of FLRS. Moreover it might yield a biomarker should it be possible to measure central HVA accurately and non-invasively, e.g. using 1H-MRS, or in plasma (possibly, the ratio of plasma HVA and 3-methoxy-4-hydroxyphenylglycol (MHPG).

When reviewing predictors of the clozapine response, Samanaite et al. (2018) also found these studies. In addition, they found a small study by Szymanski et al. (1993). Of the three studies, Samanaite et al. (2018) observed:

"lower HVA/5-HIAA concentration ratios before clozapine were associated with a greater degree of subsequent symptomatic improvement, both in the short- and longer-term (47, 48, 64). This suggests that the balance between dopamine and serotonin metabolism before clozapine administration may be predictive of clozapine response, with lower levels of dopamine metabolism relative to higher levels of serotonin metabolism being associated with better outcomes." (p.332-333)

The use of 1H-MRS to measure other biomarkers of TRS has been demonstrated with respect to elevations in glutamate in the anterior cingulate of unmedicated individuals (e.g. Mouchlianitis et al., 2016, a). This technology has also indicated an association between baseline GABA levels and working memory performance in healthy individuals (Yoon et al., 2016). An integrative view of the emerging literature on GABA and gamma oscillations suggests this may lead to the development of biomarkers which may help diagnose TRS and evaluate responses to therapy. Also, if a fundamental problem arises from a lack of inhibition in cognitive processing, for example, through a failure of entrainment of cell populations downstream and deficits in oscillatory rhythms (e.g. Kwon et al., 1999), then this could pave the way for diverse therapeutic approaches. Therefore, the measurement of GABA levels could be informative if TRS is principally characterised by a glutamatergic hypothesis with related deficits in gamma oscillations and GABA.

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APPENDICES

These appendices contain some extensive tables which are only briefly referred to in the main text, or where there is a fair degree of overlap with other information contained there. Further, as this study concerns a rare group of participants, some data is included which might be relevant, or of potential interest, to other researchers.

APPENDIX 1:

Historic Drug Exposure before the First Episode of Psychosis (1978 - 2003)

As part of the demographic assessment referred to in sections 2.5 and 3.1, exposure to "recreational" drugs prior to the onset of psychosis was considered. All participants had "passed" an initial screening question concerning their history of drug use and whether they had received treatment for addiction. They were reminded it was not necessary to answer questions and were asked if they had ever tried a drug (from a list) and if they could recall the approximate age of "first ever" use. This was subsequently related to age of first admission for psychosis from medical records (a question not asked of participants). Setting reservations aside concerning the accuracy of self-reports about distant events, the purpose was to establish whether drug use could have been a factor in the development of TRS.

Figure Appx. 1. 1 depicts the estimates that arose from this cross-tabulation and the corresponding data is found in Table Appx. 1. 1. From these, it would appear the majority of individuals, had tried "recreational drugs' before the onset of psychosis and around a third indicated they had tried at least 4 different kinds of drug. The differences between the individuals grouped according to symptom levels (PANSS scores) appears minimal, but the relatively small group sizes and the questionable quality of the data is not strong enough to make firm inferences.

When considered from the perspective of the pharmacological actions and psychotomimetic effects of the drugs (Figure Appx. 1. 2), the potential relevance to schizophrenia becomes clearer as all are agents which might alter or, otherwise, interact with a pre-existing vulnerability in circuitry associated with schizophrenia. As previously observed, certain drugs have been associated with the development of psychosis, for example, cannabis, cocaine and amphetamine are known to increase dopamine availability in the striatal synapse and the risk concerning cannabis is now well-established (Murray et al., 2017; Rapp et al., 2013). Cannabis appears to have been the most commonly used drug with 64% of

"first ever" experiences reported prior to diagnosis (one participant estimated they had been a regular user of cannabis since the age of 10 years and several may have continued or extended drug taking after diagnosis). As indicated in Figure Appx. 1. 2, 72% of TRS participants may have taken drugs which boost dopamine availability before their FEP.

Figure Appx. 1. 1 Estimated Variety of Drugs tried in the TRS Group Prior to a First Episode of Psychosis

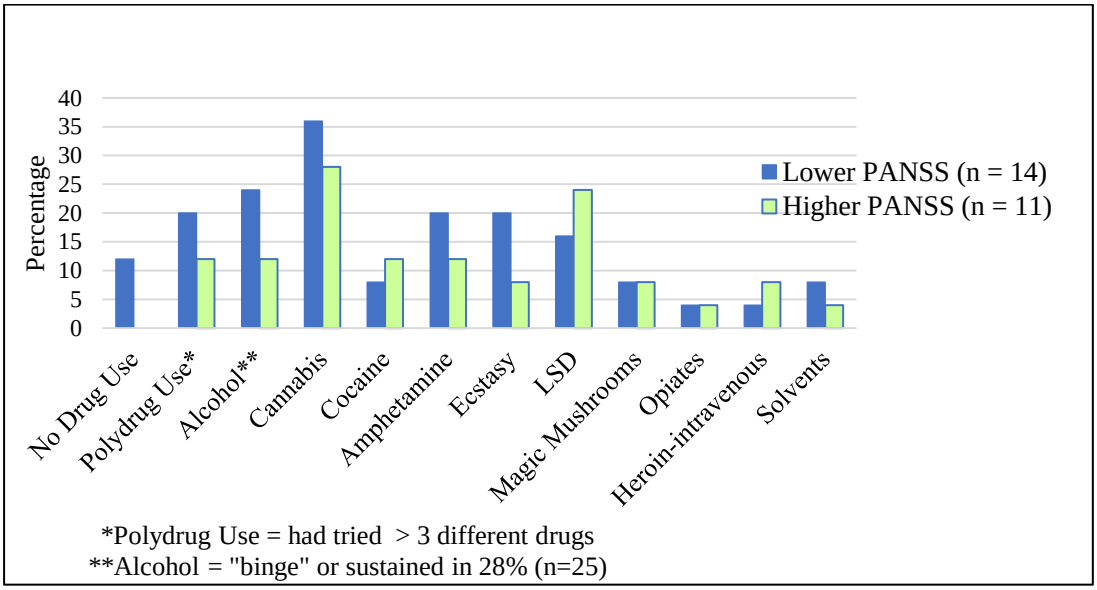
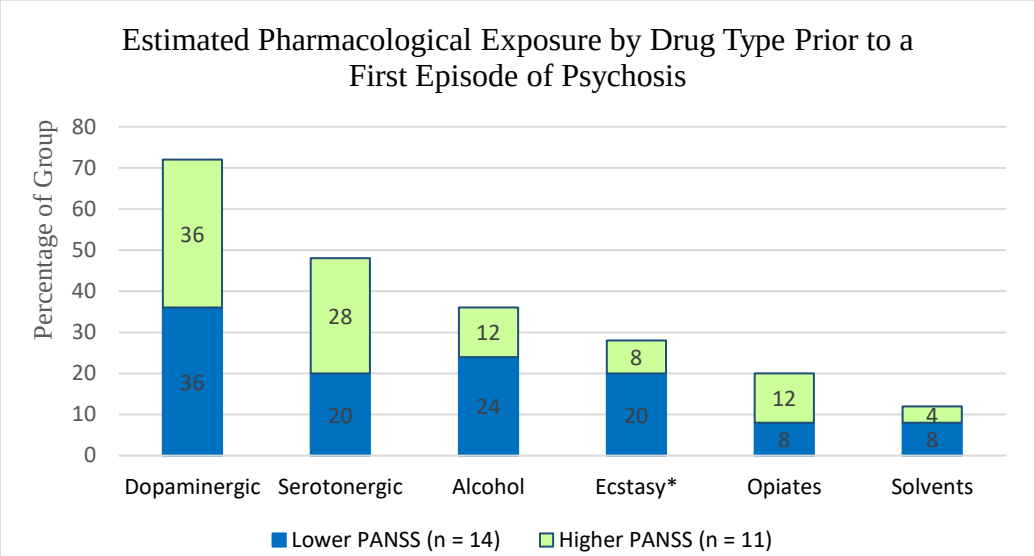


Table Appx 1. 1 Types of Drug Experienced by TRS Participants Before a First Episode of Psychosis - Grouped by Level of Symptoms and Combined*

	Lower PANSS %	Higher PANSS %	Groups Combined %
No Drug Use	12	0	12
Polydrug Use**	20	12	32
Alcohol***	24	12	36
Cannabis	36	28	64
Cocaine¬	8	12	20
Amphetamine	20	16	36
Ecstasy (MDMA)	20	8	28
LSD	16	24	40
Magic Mushrooms	8	8	16
Opiates	4	4	8
Heroin (intravenous)	4	8	12
Solvents	8	4	12

* Percentages all shown in relation to entire whole group (n = 25)
**Polydrug Use - tried four or more different kinds of drug
*** Alcohol Use - only noted if binge drinking (28% of all TRS) or sustained use (8%).
¬ includes 1 case of crack cocaine use.

Figure Appx. 1. 2 Estimated Pharmacological Exposure by Drug Type to TRS Participants Before the First Episode of Psychosis



NB: Numbers inside the columns indicate percentage out of group (n=25) per class;

The data in each column represents pharmacological exposure, and was counted only once for an individual, irrespective of the number of different drugs that may have been tried within a particular class.

* Ecstasy has notable serotonergic and dopaminergic effects.

Alcohol = glutamatergic; Cannabis, Cocaine and Amphetamine = dopaminergic; LSD and "magic mushrooms" (Psilocybin) = serotonergic; Ecstasy (MDMA) = dopaminergic and serotonergic; Heroin and Opium = opiates. Solvents unspecified.

The high level of serotonergic agents tried by 48% of the clinical participants is also interesting as during a period when LSD use was legal on both sides of the Atlantic, many cases of psychosis were associated with its use (Grof 1975). Clozapine has been demonstrated to have antagonistic effects at certain serotonin receptors and treatment might even lead to a downregulation (e.g. Hietala et al. (1992). Further, 28% of TRS participants indicated the use of ecstasy (3,4-Methylenedioxymethamphetamine, or MDMA), which has notable effects on both dopamine and serotonin systems. Alcohol, which has glutamatergic effects, can be highly excitotoxic, particularly, during vulnerable periods, as observed in offspring with foetal alcohol syndrome. Of those who had age of alcohol use had predated the first onset of illness, 28% of the group (i.e. 7/9 participants) described periods of "binge" drinking, or consuming large quantities for a regular period.

Some clues as to LSD's biological and psychotropic effects comes from research by Muthukumaraswamy et al. (2013) with a related drug, psilocybin, a nonselective agonist at a serotonin (5HT2A) receptor. In healthy individuals, this was observed to reduce the power of intrinsic oscillations in frontal association cortices, posterior association cortices and the default mode network. Further, through dynamic causal modelling of cell populations it was determined that an increase in the excitability of deep-layer neurons which have a high density of 5HT2A receptors in the cingulate cortex explained desynchronization in a major hub of the DMN, the posterior cingulate cortex. This was consistent with previous work in the area by this group, who concluded "breakdown of brain networks may be a fundamental feature of the psychedelic state."

The use of MDMA ("ecstasy") is also concerning, as a pure substance, for example, dopaminergic terminals in striosomes of the mouse striatum were observed to be vulnerable to loss after MDMA administration (Granado et al., 2008) In a further study, Granado et al. (2010) observed depletions in tyrosine hydroxylase following metamphetamine, particularly in the striosomes rather than the matrix of the basal ganglia, commenting this pattern is similar to the effects of neurotoxins used in models of PD and early Huntingdon's.
In addition to the dopaminergic and serotonergic effects, cheaper drugs have often been mixed in during manufacture to dilute the drug (e.g. one study which analysed 25 ecstasy tablets from around the UK found high doses of ketamine in 2 tablets.[61]
Therefore "ecstasy" either as pure MDMA, or combined with other substances and, perhaps, in the context of potentiated release of very high levels of cortisol on the dance-floor (Parrott, 2008, 2009), could surely be neurotoxic?

These observations may not be unusual in schizophrenia research although illicit drug use may be under-reported: for example, in the US-based multi-centre CATIE study of 1042 individuals, 38% tested positive for at least one of three drug types (cannabis, cocaine and metamphetamine), although 58% of these did not disclose this in self-rated assessments (Bahorik et al., 2014). In a further study of 974 individuals, Bahorik et al. (2014) observed there were no improvements in cognition associated with positive drug screening tests, indeed quite the reverse for cocaine, which was associated with reduced processing speed, while amphetamine at low dose increased it moderately. However, generally, no significant differences in cognition were observed between individuals with schizophrenia who tested

[61] Other contaminants found in some tablets were the stimulants caffeine, amphetamine, amphetamine and ephedrine. Paracetamol had also been used as "cutting agent" although "not present in concentrations likely to cause harm, even if individuals took several tablets in one evening." Sherlock et al., 1999, p.196.

positive for drug use (cannabis, cocaine and methamphetamine) and those who tested negatively; however, this does not exclude the possibility of impairment with other types of drug such as ketamine or PCP (both NMDA antagonists) or LSD (serotonergic).

This data may reflect drug taking patterns in S.E. London generally and, what was available over a 25-year period from around 1978-2003 (the earliest first diagnosis in the cohort was in 1985 and last was in 2003). The NMDA antagonist ketamine which can induce schizophrenia-like symptoms was not on the list asked of participants but may have become popular only towards the end of this period[62] (except when used to dilute ecstasy).

[62] Ketamine was described in one memoir as "the new kid on the block" in 2003 ... Ecstasy had been the drug of choice in the '90s, LSD felt like a relic from the '60s, and mushrooms were as old as the hills." Article by Zoe Cormier "The Rise and Rise of Ketamine" https://medium.com/s/story/the-rise-and-rise-of-ketamine-644b0aba9cb3

APPENDIX 2

Tables of Within Group Activations Relative to the Baseline ('Is it X?')

- Within Control Group Significant Increases

Table Appx. 2. 1.1 Within Control Group: areas exhibiting significant increases in activation relative to the baseline task ('Is it X?') during the 1-Back condition

Anatomical Location	Brodmann Area	Hemis-phere	Cluster size (mm^3)	p-Value	Talairach co-ordinates* x	y	z
Inferior Frontal Gyrus	-	R	155	0.0030	40	52	0
Middle Frontal Gyrus	BA 10	L	96	0.0041	-33	44	17
Middle Frontal Gyrus	BA 10	R	384	0.0015	36	37	23
Precentral Gyrus	BA 9	L	117	0.0036	-43	22	36
Insula	BA 13	L	129	0.0036	-33	15	10
Middle Frontal Gyrus	BA 6	R	461	0.0005	28	9	55
Inferior Frontal Gyrus	BA 9	R	205	0.0012	43	4	26
Middle Frontal Gyrus	BA 6	L	268	0.0015	-28	0	50
Thalamus	-	R	193	0.0041	11	-7	3
Thalamus	-		87	0.0055	-18	-15	10
Midbrain, Substantia Nigra (10.0mm away)	-	R	19	0.0071	10	-20	-10
Superior Temporal Gyrus	BA 22	L	37	0.0045	-51	-37	10
Temporal Lobe, Sub-Gyral	-	R	324	0.0030	47	-41	-7
Parietal lobe, subgyral	BA 7	R	313	0.0002	37	-44	33
(Posterior) Cingulate Gyrus	BA 31	L	214	0.0021	-19	-44	37
Parahippocampal Gyrus	BA 19	L	142	0.0036	-40	-44	-7
Cerebellum, Anterior Lobe, Culmen	-	L	104	0.0061	-40	-48	-20
Cerebellum, Anterior Lobe, Culmen	-	L	24	0.0066	0	-52	-13
Temporal Lobe, Fusiform Gyrus	BA 37	R	266	0.0016	40	-59	-10
Precuneus	BA 7	R	35	0.0004	23	-63	30
Temporal Lobe, Fusiform Gyrus	BA 37	L	223	0.0021	-40	-63	-11
Posterior Cingulate	BA 18	L	185	0.0013	-25	-67	16
Superior Parietal Lobule	BA 7	L	37	0.0047	-22	-74	44
Occipital Lobe, Lingual Gyrus	BA 18	R	201	0.0023	25	-74	-10

24 clusters ordered from anterior to posterior in the coronal plane.

Table Appx. 2. 1.2 Within Control Group: areas exhibiting significant increases in activation relative to the baseline task ('Is it X?') during the 2-Back condition

Anatomical Location	Brodmann Area	Hemis -phere	Cluster size (mm^3)	p-Value	Talairach co-ordinates*		
					x	y	z
Middle Frontal Gyrus	BA 10	R	408	0.00000	40	59	13
Superior Frontal Gyrus	BA 10	L	385	0.00001	-36	48	20
Superior Frontal Gyrus	BA 9	R	432	0.00000	40	37	30
Inferior Frontal Gyrus	BA 13	R	350	0.00002	33	22	7
Claustrum	-	L	276	0.00001	-25	22	7
Middle Frontal Gyrus	BA46	L	460	0.00000	-40	19	23
Superior Frontal Gyrus	BA 6	L	310	0.00000	0	7	50
Inferior Frontal Gyrus	BA 9	R	279	0.00000	43	4	23
Superior Frontal Gyrus	BA 6	L	410	0.00000	-25	4	50
Frontal Lobe, Sub-Gyral	BA 6	R	529	0.00000	25	4	53
Thalamus, Anterior Nucleus	BA	L	399	0.00014	-11	-4	7
Thalamus	-	R	412	0.00015	11	-4	3
Brainstem: Substantia Nigra (9.8mm away)	-	R	147	0.00121	12	-16	-10
Superior Temporal Gyrus	BA 22	R	542	0.00019	43	-26	-3
Temporal Lobe, Fusiform Gyrus	BA 37	L	859	0.00014	-40	-44	-10
Cerebellum, Anterior Lobe, Cerebellar Lingual	-	R	163	0.00082	0	-44	-17
Inferior Parietal Lobule (6.4 mm away)	BA 40	R	585	0.00000	36	-45	40
Cerebellum, Anterior Lobe	-	R	208	0.00008	29	-56	-30
Middle Temporal Gyrus (10.0 mm away from grey)	BA 39	L	421	0.00001	-31	-57	29
Cerebellum, Posterior Lobe, Cerebellar Tonsil	-	L	402	0.00008	-36	-59	-33
Posterior Cingulate (5.8 mm away)	BA 31	R	536	0.00000	21	-62	17
Precuneus	BA 7	L	533	0.00000	-21	-63	33
Cerebellum, Posterior Lobe, Uvula,	-	L	161	0.00107	-11	-63	-33
Occipital Lobe, Lingual Gyrus,	BA 19	R	291	0.00027	29	-63	0
Cerebellum, Posterior Lobe, Declive	-	R	213	0.00301	4	-67	-20
Cerebellum, Posterior Lobe, Declive	-	R	214	0.00024	33	-67	-17

26 clusters ordered from anterior to posterior in the coronal plane.

Table Appx. 2. 1.3 Within Control Group: areas exhibiting significant increases in activation relative to the baseline task ('Is it X?') during the 3-Back condition

Anatomical Location	Brodmann Area	Hemis-phere	Cluster size (mm^3)	p-Value	Talairach co-ordinates*		
					x	y	z
Middle Frontal Gyrus	BA 10	R	390	0.00000	40	56	13
Middle Frontal Gyrus	BA 10	L	511	0.00001	-36	37	23
Middle Frontal Gyrus	BA 9	R	399	0.00000	36	37	33
Inferior Frontal Gyrus	BA 45	R	505	0.00001	29	30	7
Claustrum	-	L	455	0.00001	-25	26	3
Middle Frontal Gyrus	BA 9	L	343	0.00000	-47	19	36
Inferior Frontal Gyrus, (5.2 mm away)	BA 9	R	331	0.00001	46	10	26
Superior Frontal Gyrus	BA 6	L	374	0.00000	-4	4	53
Frontal Lobe, Sub-Gyral	BA 6	L	337	0.00000	-25	0	53
Frontal Lobe, Sub-Gyral	BA 6	R	495	0.00000	27	-1	55
Thalamus	-	R	518	0.00003	11	-4	3
Thalamus, Ventral Lateral Nucleus	-	L	456	0.00022	-11	-11	10
Brainstem: Substantia Nigra (10.0 mm away)	-	R	190	0.00061	10	-16	-10
Middle Temporal Gyrus	BA 20	R	538	0.00021	51	-37	-10
Parietal Lobe, Sub-Gyral	BA 40	R	911	0.00000	36	-44	33
Parahippocampal Gyrus (7.3 mm away)	BA 19	L	496	0.00027	-37	-44	-3
Cerebellum, Anterior Lobe, Cerebellar Lingual	-	R	164	0.00084	0	-45	-17
Fusiform Gyrus	BA 37	L	329	0.00044	-40	-48	-17
Cerebellum, Posterior Lobe, Cerebellar Tonsil	-	R	197	0.00086	33	-52	-33
Cerebellum, Posterior Lobe, Cerebellar Tonsil	-	L	258	0.00023	-33	-56	-33
Middle Temporal Gyrus (6.7 mm away)	BA 37	R	481	0.00073	40	-56	0
Precuneus, (10.0 mm away)	BA 19	L	694	0.00002	-31	-62	42
Cerebellum, Posterior Lobe, Uvula	-	L	369	0.00100	-11	-63	-30
Posterior Cingulate	BA 30	L	328	0.00022	-29	-70	13

24 clusters ordered from anterior to posterior in the coronal plane.

- ***Within Control Group Significant Decreases***

Table Appx. 2. 1.4 Within Control Group: areas exhibiting significant decreases in activation relative to the baseline task ('Is it X?') during the 1-Back condition

Anatomical Location	Brodmann Area	Hemis-phere	Cluster size (mm^3)	p-Value	Talairach co-ordinates* x	y	z
Medial Frontal Gyrus	BA 10	L	122	0.00432	-14	33	-6
Superior Frontal Gyrus	BA 9	R	543	0.00013	4	56	23
Superior Frontal Gyrus	BA 9	L	421	0.00013	-11	52	36
Anterior Cingulate	-	R	147	0.00224	4	48	0
Superior Frontal Gyrus	BA 6	L	415	0.00131	-11	30	56
Superior Temporal Gyrus	BA 38	L	175	0.00150	-40	19	-30
Sub-lobar Extra-Nuclear	BA 13	L	65	0.00522	-25	19	-10
Superior Temporal Gyrus	BA 22	R	39	0.00331	54	11	0
Superior Temporal Gyrus	BA 22	L	10	0.00720	-61	11	-3
Middle Temporal Gyrus	BA 21	R	289	0.00263	43	7	-30
Cingulate Gyrus	BA 24	R	259	0.00117	7	7	33
Superior Temporal Gyrus	BA 21	L	28	0.00752	-54	-4	3
Cingulate Gyrus	BA 24	L	265	0.00007	0	-11	40
Parahippocampal Gyrus	BA 28	L	82	0.00718	-18	-15	-13
Postcentral Gyrus (nearest grey 5.2mm away)	BA 2	R	224	0.00315	58	-22	23
Postcentral Gyrus	BA 1	L	24	0.00440	-65	-22	23
Insula	BA 13	R	127	0.00340	43	-22	17
Postcentral Gyrus	BA 2	L	122	0.00517	-44	-22	30
Posterior Cingulate Gyrus	BA 31	L	254	0.00032	-7	-30	40
Inferior Parietal Lobule	BA 40	L	134	0.00501	-36	-37	50
Postcentral Gyrus	BA 5	R	24	0.00341	40	-41	63
Posterior Cingulate Gyrus	BA 31	L	661	0.00030	-7	-44	33
Precuneus	BA 7	L	143	0.00402	-7	-48	59
Precuneus,	BA 19	L	113	0.00371	-43	-74	36
Middle Temporal Gyrus	BA 39	L	118	0.00189	43	-59	10
Inferior Parietal Lobule	BA 40	L	59	0.00420	-58	-59	40
Middle Occipital Gyrus (BA 18 is sometimes described as the Posterior Cingulate)	BA 18	R	51	0.00389	14	-92	17

27 clusters ordered from an anterior to posterior in the coronal plane.

Table Appx. 2. 1.5 Within Control Group: areas exhibiting significant decreases in activation relative to the baseline task ('Is it X?') during the 2-Back condition

Anatomical Location	Brodmann Area	Hemis-phere	Cluster size (mm^3)	p-Value	Talairach co-ordinates*		
					x	y	z
Superior Frontal Gyrus	BA 10	R	1260	0.00000	4	59	26
Superior Frontal Gyrus	BA 8	L	730	0.00000	-15	30	46
Superior Temporal Gyrus	BA 38	L	599	0.00008	-36	15	-23
Superior Temporal Gyrus	BA 38	R	415	0.00011	43	11	-30
Cingulate Gyrus	BA 24	R	387	0.00004	7	7	33
Putamen	-	L	578	0.00055	-18	4	-10
Precentral Gyrus	BA 43	R	338	0.00006	51	-4	10
Claustrum	-	R	543	0.00051	36	-4	-7
Precentral Gyrus	BA 6	L	221	0.00054	-51	-7	7
Superior Temporal Gyrus	BA 22	L	251	0.00134	-51	-7	-7
Claustrum	-	L	344	0.00014	-33	-11	13
Cingulate Gyrus	BA 24	L	599	0.00000	-4	-15	33
Insula	BA 13	R	809	0.00000	47	-26	23
Cingulate Gyrus	BA 31	L	2233	0.00000	-7	-33	36
Middle Temporal Gyrus	BA 39	L	676	0.00033	-43	-56	10
Cerebellum, Posterior Lobe, Inferior Semi-Lunar Lobule	-	R	261	0.00032	29	-74	40

16 clusters ordered from an anterior to posterior in the coronal plane.

Table Appx. 2. 1.6 Within Control Group: areas exhibiting significant decreases in activation relative to the baseline task ('Is it X?') during the 3-Back condition

Anatomical Location	Brodmann Area	Hemis-phere	Cluster size (mm^3)	p-Value	Talairach co-ordinates*		
					x	y	z
Superior Frontal Gyrus	BA 9	L	2191	0.00000	-4	48	30
Superior Temporal Gyrus	BA 38	L	812	0.00015	-33	11	-30
Middle Temporal Gyrus	BA 21	R	696	0.00089	36	4	-30
Claustrum	-	L	720	0.00039	-33	-7	13
Precentral Gyrus	BA 4	R	618	0.00000	47	-15	43
Parahippocampal Gyrus	BA 28	L	529	0.00101	-22	-15	-13
Cingulate Gyrus	BA 24	R	1687	0.00000	4	-19	40
Insula	BA 13	R	769	0.00001	47	-22	20
Precentral Gyrus (8.1 mm away)	BA 4	L	728	0.00000	-25	-28	48
Postcentral Gyrus	BA 3	L	544	0.00000	-22	-33	59
Cerebellum, Anterior Lobe, Culmen	-	R	304	0.00131	22	-37	-17
Parietal Lobe, Supramarginal Gyrus	BA 40	L	172	0.00301	-61	-48	33
Middle Temporal Gyrus	BA 39	L	201	0.00062	-43	-56	10
Cuneus	BA 17	R	733	0.00025	11	-85	7

14 clusters ordered from an anterior to posterior in the coronal plane.

Tables of Within TRS Group Activations Relative to the Baseline ('Is it X?')

- Within TRS Group Significant Increases

Table Appx. 2. 2.1 Within TRS Group: areas exhibiting significant increases in activation relative to the baseline task ('Is it X?') during the 1-Back condition

Anatomical Location	Brodmann Area	Hemis-phere	Cluster size (mm^3)	p-Value	Talairach co-ordinates*		
					x	y	z
Middle Frontal Gyrus (nearest grey 6.9mm away)	BA 10	R	296	0.00075	36	45	11
Middle Frontal Gyrus	BA 10	L	331	0.00108	-36	41	13
Middle Frontal Gyrus	BA 46	R	104	0.00193	43	33	23
Middle Frontal Gyrus	BA 9	L	111	0.00380	-40	26	33
Precentral Gyrus	BA 44	R	64	0.00395	51	15	7
Middle Frontal Gyrus	BA 9	R	86	0.00305	43	11	33
Superior Frontal Gyrus	BA 6	L	207	0.00164	-4	7	56
Precentral Gyrus	BA 6	L	166	0.00118	-40	0	30
Middle Frontal Gyrus	BA 6	L	99	0.00435	-29	0	56
Frontal Lobe, Sub-Gyral	BA 6	R	164	0.00109	29	-4	53
Thalamus	-	L	59	0.00471	-11	-7	0
Thalamus, Ventral Lateral Nucleus	-	R	121	0.00664	14	-11	10
Thalamus, Medial Dorsal Nucleus	-	L	44	0.00692	-7	-22	10
Middle Temporal Gyrus (nearest grey 5.7 mm away)	BA 20	R	94	0.00339	51	-37	-11
Inferior Parietal Lobule	BA 40	R	265	0.00022	40	-44	40
Fusiform Gyrus	BA 37	R	126	0.00266	47	-48	-17
Cerebellum, Posterior Lobe, Declive	-	L	137	0.00334	-51	-52	-20
Cerebellum, Posterior Lobe, Cerebellar Tonsil	-	R	91	0.00459	36	-56	-36
Middle Temporal Gyrus (nearest grey 5.2 mm away)	BA 39	L	516	0.00016	-31	-57	29
Precuneus	BA 7	R	176	0.00140	14	-67	46

20 clusters ordered from anterior to posterior in the coronal plane.

Table Appx. 2. 2.2 Within TRS Group: areas exhibiting significant increases in activation relative to the baseline task ('Is it X?') during the 2-Back condition.

Anatomical Location	Brodmann Area	Hemis-phere	Cluster size (mm^3)	p-Value	Talairach co-ordinates* x	y	z
Middle Frontal Gyrus (nearest grey 5.2 mm away)	BA 10	R	338	0.00001	39	47	10
Temporal Lobe, Sub-Gyral (nearest grey 6.4 mm away)	BA 37	R	405	0.00006	47	45	-7
Middle Frontal Gyrus	BA 10	L	550	0.00001	-36	41	13
Middle Frontal Gyrus	BA 10	R	209	0.00003	33	41	20
Middle Frontal Gyrus	BA 9	R	163	0.00001	41	33	34
Middle Frontal Gyrus	BA 9	L	227	0.00003	-40	30	30
Insula	BA 45	R	414	0.00006	29	26	7
Insula	BA 13	L	333	0.00002	-36	20	8
Medial Frontal Gyrus	BA 6	R	263	0.00001	6	16	44
Inferior Frontal Gyrus	BA 9	R	248	0.00007	40	7	26
Putamen	-	L	289	0.00050	-14	3	7
Precentral Gyrus	BA 6	L	280	0.00001	-40	0	30
Frontal Lobe, Sub-Gyral	BA 6	L	380	0.00000	-22	0	56
Medial Globus Pallidus,	-	R	379	0.00138	11	-4	0
Middle Frontal Gyrus	BA 6	R	259	0.00000	25	-7	50
Inferior Parietal Lobule (nearest grey 7.7 mm away)	BA 40	L	461	0.00000	-35	-47	38
Angular Gyrus	BA 39	R	585	0.00000	33	-56	36
Cerebellum, Posterior Lobe, Declive	-	L	463	0.00077	-40	-56	-20
Cerebellar Tonsil	-	L	199	0.00033	-40	-59	-33
Cerebellum, Posterior Lobe, Cerebellar Tonsil	-	R	330	0.00015	36	-63	-33
Precuneus	BA 7	L	385	0.00004	-14	-67	43
Cerebellum, Posterior Lobe, Uvula	-	L	290	0.00068	-7	-74	-33
Fusiform Gyrus	BA 19	R	184	0.00233	33	-78	-13

23 clusters ordered from anterior to posterior in the coronal plane.

Table Appx. 2. 2.3 Within TRS Group: areas exhibiting significant increases in activation relative to the baseline task ('Is it X?') during the 3-Back condition

Anatomical Location	Brodmann Area	Hemis-phere	Cluster size (mm^3)	p-Value	Talairach co-ordinates*		
					x	y	z
Middle Frontal Gyrus	BA 10	R	66	0.00001	25	56	10
Superior Frontal Gyrus	BA 11	R	46	0.00696	11	48	-13
Middle Frontal Gyrus	BA 10	L	411	0.00001	-36	41	13
Middle Frontal Gyrus	BA 9	R	276	0.00002	40	33	30
Middle Frontal Gyrus	BA 9	L	216	0.00001	-40	30	30
Insula	BA 13	R	445	0.00005	33	22	3
Insula	BA 13	L	378	0.00007	-33	19	7
Middle Frontal Gyrus	BA 9	R	207	0.00008	50	14	26
Medial Frontal Gyrus	BA 6	R	345	0.00000	4	14	46
Inferior Frontal Gyrus	BA 9	L	270	0.00001	-40	4	30
Caudate Body	-	L	243	0.00034	-14	4	13
Frontal Lobe, Sub-Gyral	BA 6	R	249	0.00000	29	0	53
Middle Frontal Gyrus	BA 6	L	298	0.00002	-25	-4	46
Hypothalamus	-	R	487	0.00143	7	-7	-3
Middle Temporal Gyrus	BA 21	L	64	0.00440	-58	-19	-7
Middle Temporal Gyrus	BA 21	R	235	0.00114	58	-26	-10
Superior Temporal Gyrus	BA 22	L	85	0.00250	-58	-41	10
Inferior Parietal Lobule	BA 40	R	435	0.00001	36	-48	36
Inferior Parietal Lobule	BA 40	L	276	0.00000	-47	-48	36
Fusiform Gyrus	BA 37	L	328	0.00040	-51	-48	-20
Precuneus	BA 7	L	529	0.00006	-14	-67	43
Cerebellum, Posterior Lobe, Tuber	-	R	374	0.00040	36	-67	-26
Cerebellum, Posterior Lobe, Uvula	-	L	216	0.00089	-7	-78	-33

23 clusters ordered from anterior to posterior in the coronal plane.

- ***Within TRS Group Significant Decreases***

Table Appx. 2. 2.4 Within TRS Group: areas exhibiting significant decreases in activation relative to the baseline task ('Is it X?') during the 1-Back condition

Anatomical Location	Brodmann Area	Hemis-phere	Cluster size (mm^3)	p-Value	Talairach co-ordinates*		
					x	y	z
Superior Frontal Gyrus	BA 9	R	94	0.00155	7	56	28
Superior Frontal Gyrus	BA 9	L	117	0.00168	-7	56	26
Medial Frontal Gyrus	BA	R	208	0.00248	7	52	13
Superior Frontal Gyrus	BA 8	R	17	0.00591	13	47	47
Superior Frontal Gyrus	BA 8	L	204	0.00184	-10	37	43
Cingulate Gyrus	BA 24	L	449	0.00083	-15	36	-0
Superior Frontal Gyrus	BA 8	R	93	0.00262	22	33	43
Inferior Frontal Gyrus (nearest grey 6.9mm away)	BA 47	R	48	0.00322	57	23	-3
Superior Temporal Gyrus	BA 38	L	65	0.00566	-43	11	-26
Middle Temporal Gyrus	BA 21	L	47	0.00151	-58	4	13
Middle Temporal Gyrus	BA 21	R	82	0.00381	54	0	-17
Precentral Gyrus (nearest grey 6.9mm away)	BA 6	R	212	0.00445	47	-11	30
Superior Temporal Gyrus	BA 42	R	38	0.00221	69	-30	17
Precentral Gyrus	BA 4	L	292	0.00162	-29	-30	59
Cerebellum, Anterior Lobe, Culmen	-	L	50	0.00830	-25	-33	-30
Parahippocampal Gyrus	BA 36	L	79	0.00686	-22	-33	-13
Cerebellum, Anterior Lobe	-	R	82	0.00530	22	-33	-26
Cingulate Gyrus	BA 31	L	330	0.00045	-11	-41	30
Posterior Cingulate	BA 23	R	411	0.00058	7	-44	26
Parahippocampal Gyrus	BA 30	L	151	0.00211	-11	-45	3
Cerebellum, Anterior Lobe, Culmen	-	R	176	0.00277	11	-48	0
Middle Temporal Gyrus	BA 22	R	129	0.00557	54	-48	3
Cerebellum, Anterior Lobe	-	R	70	0.00917	4	-52	-26
Middle Temporal Gyrus	BA 39	L	107	0.00288	-47	-67	23
Lingual Gyrus	BA 18	R	117	0.00533	11	-78	-3
Lingual Gyrus	BA 18	R	90	0.00434	18	-78	0

26 clusters ordered from an anterior to posterior in the coronal plane.

Table Appx. 2. 2.5 Within TRS Group: areas exhibiting significant decreases in activation relative to the baseline task ('Is it X?') during the 2-Back condition

Anatomical Location	Brodmann Area	Hemis-phere	Cluster size (mm^3)	p-Value	Talairach co-ordinates*		
					x	y	z
Medial Frontal Gyrus	BA 9	R	586	0.00002	0	52	13
Cingulate Gyrus (Dorsal PCC)	BA 31	R	1136	0.00000	11	-40	30
Medial Frontal Gyrus	BA 8	L	585	0.00009	-14	33	43
Inferior Frontal Gyrus	BA 9	R	93	0.00033	65	19	30
Superior Temporal Gyrus	BA 38	R	192	0.00248	47	15	-23
Middle Temporal Gyrus	BA 21	L	236	0.00226	-43	4	-23
Middle Temporal Gyrus	BA 21	L	130	0.00137	-58	4	-13
Cingulate Gyrus (Anterior)	BA 24	R	951	0.00000	0	-11	40
Postcentral Gyrus,	BA 3	L	261	0.00006	-51	-19	36
Precentral Gyrus	BA 4	L	549	0.00000	-36	-20	40
Insula	BA 13	L	367	0.00026	-43	-26	13
Superior Temporal Gyrus	BA 42	R	183	0.00101	69	-30	17
Hippocampus	-	L	187	0.00093	-29	-30	-7
Cerebellum, Anterior Lobe, Culmen	-	L	109	0.00210	-22	-30	-26
Cerebellum, Anterior Lobe	-	R	254	0.00084	22	-37	-26
Precuneus	BA 31	L	639	0.00000	-14	-48	30
Parahippocampal Gyrus	BA 30	L	823	0.00005	-11	-48	3
Cerebellum, Anterior Lobe, Dentate	-	L	78	0.00126	-14	-48	-23
Cerebellum, Anterior Lobe	-	L	229	0.00064	-7	-48	-0
Middle Temporal Gyrus	BA 39	L	173	0.00101	-47	-70	13

20 clusters ordered from an anterior to posterior in the coronal plane.

Table Appx. 2. 2.6 Within TRS Group: areas exhibiting significant decreases in activation relative to the baseline task ('Is it X?') during the 3-Back condition

Anatomical Location	Brodmann Area	Hemis-phere	Cluster size (mm^3)	p-Value	Talairach co-ordinates*		
					x	y	z
Medial Frontal Gyrus	BA 9	L	767	0.00021	-7	52	33
Superior Frontal Gyrus	BA 8	R	321	0.00051	17	44	46
Superior Temporal Gyrus	BA 38	R	36	0.00304	33	22	26
Superior Temporal Gyrus	BA 38	R	68	0.00216	47	11	23
Middle Temporal Gyrus	BA 38	L	218	0.00185	-43	7	23
Middle Temporal Gyrus	BA 21	R	19	0.00303	61	0	20
Cingulate Gyrus (Anterior)	BA 24	L	916	0.00000	-5	-17	42
Postcentral Gyrus	BA 3	R	565	0.00000	40	-22	40
Superior Temporal Gyrus	BA 41	R	1247	0.00017	47	-26	17
Transverse Temporal Gyrus	BA 41	L	843	0.00025	-36	-26	13
Cingulate Gyrus (Posterior)	BA 31	R	1036	0.00000	18	-30	43
Cingulate Gyrus (Posterior)	BA 31	L	1032	0.00000	-14	-37	36
Parahippocampal Gyrus	BA 36	L	144	0.00409	-25	-37	13
Cerebellum, Anterior Lobe, Culmen	-	R	549	0.00113	11	-44	13
Cerebellum, Posterior Lobe, Tonsil, (6.9 mm away)	-	L	126	0.00590	-11	-45	32
Lingual Gyrus	BA 18	L	563	0.00001	-14	-52	3
Cerebellum, Posterior Lobe, Declive	-	L	102	0.00372	-14	-59	13
Middle Temporal Gyrus	BA 39	L	199	0.00082	-47	-70	17
Lingual Gyrus	-	L	671	0.00013	-7	-78	0

19 clusters ordered from an anterior to posterior in the coronal plane.

APPENDIX 3:

Factorial Analysis (TRS and Controls) using the voxel p-Value of 0.01

Table Appx. 3. 1 Factorial ANCOVAs comparing the haemodynamic response in TRS and Control Groups using a voxel p-Value of 0.01

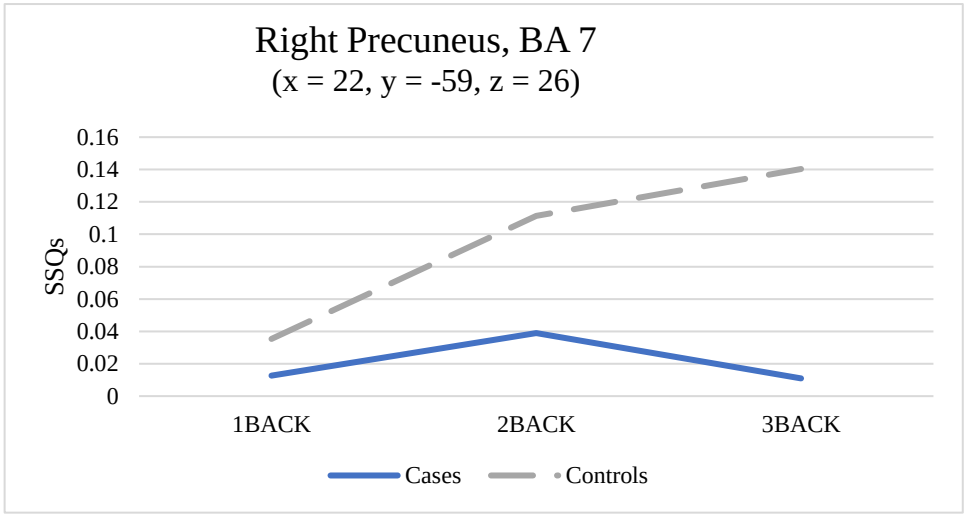
Anatomical Location	Brodmann Area	Hemis-phere	Cluster size (mm^3)	p-Value	Talairach co-ordinates*		
					x	y	z
Superior Frontal Gyrus	BA 6	L	93	0.00594	0	4	50
Precuneus	BA 7	R	172	0.00264	22	-59	26

NB: Age was a covariate; threshold used voxel p value = 0.1

Anatomical Location	Brodmann Area	Hemis-phere	Cluster size (mm^3)	p-Value	Talairach co-ordinates*		
					x	y	z
Medial Frontal Gyrus	BA 8	L	271	0.00064	-4	52	40
Cingulate Gyrus (6.9mm away from nearest grey)	BA 31	L	195	0.00128	-7	-30	33

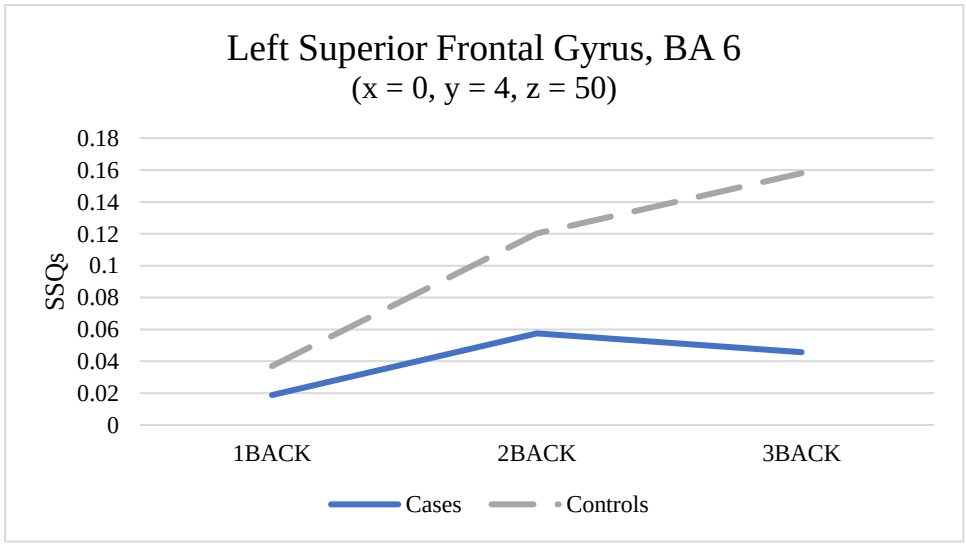
NB: Age was a covariate; threshold used voxel p value = 0.1

Figure Appx 3. 1 Haemodynamic response in the right Precuneus (BA 7) at different levels of cognitive load in TRS individuals compared with Controls



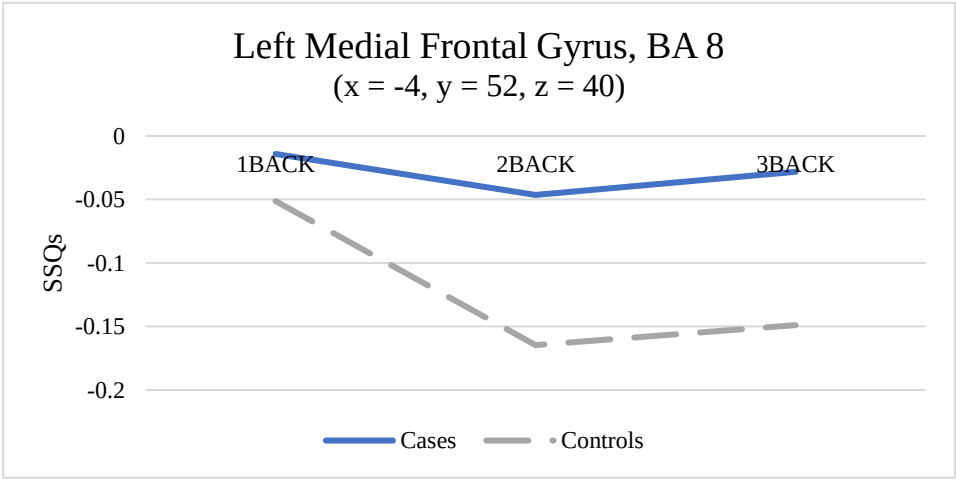
R Precuneus, BA7	1-Back	2-Back	3-Back
TRS Group	0.012699	0.038963	0.010952
Control Group	0.035352	0.111436	0.140326
* Significant at p = 0.00594			

Figure Appx 3. 2 Haemodynamic response in the left Superior Frontal Gyrus (BA 6) at different levels of cognitive load in TRS individuals compared with Controls



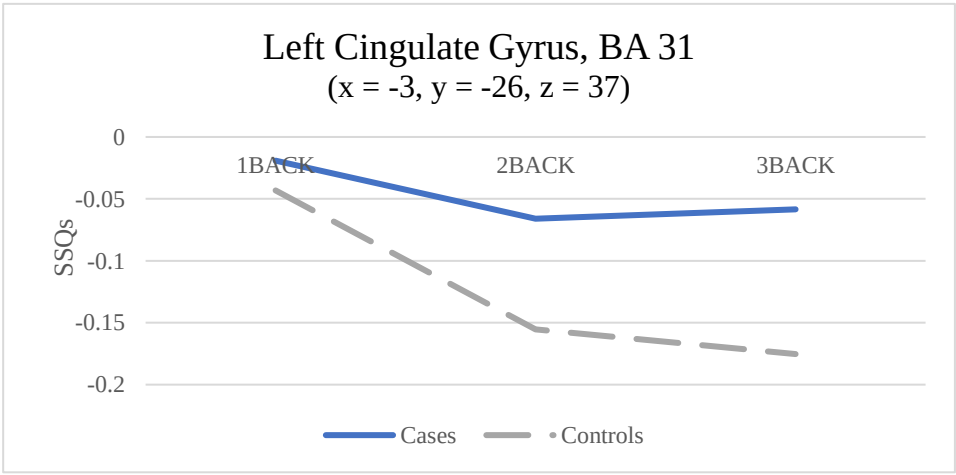
	1-Back	2-Back	3-Back
TRS Group	0.01881	0.05745	0.04568
Control Group	0.03695	0.12027	0.15800
* Significant at p = 0.00594			

Figure Appx 3. 3 Haemodynamic response in the left Medial Frontal Gyrus (BA 8) at different levels of cognitive load in TRS individuals compared with Controls



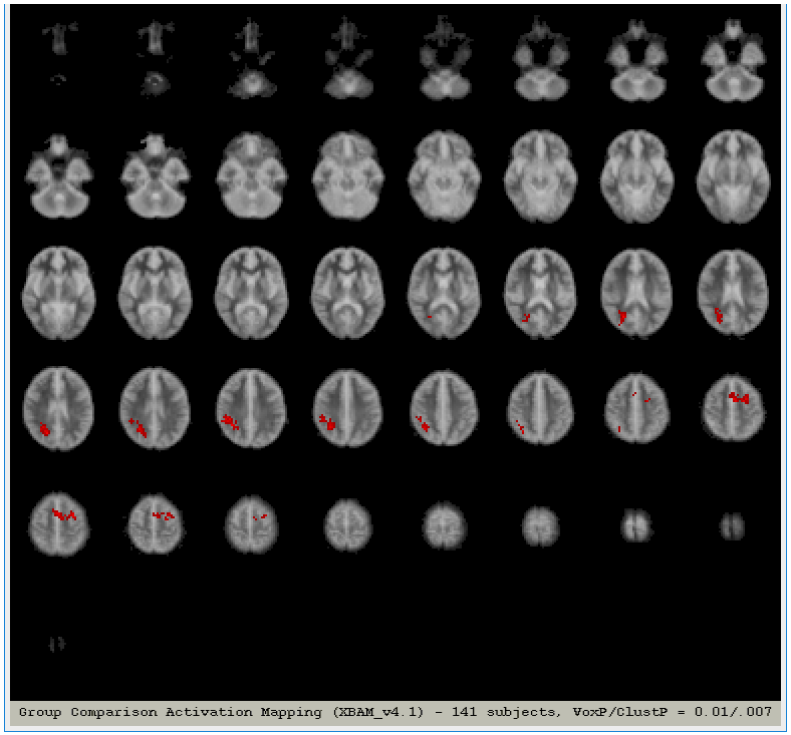
	1-Back	2-Back	3-Back
TRS Group	-0.01418	-0.04640	-0.02808
Control Group	-0.05127	-0.16462	-0.14883
* Significant at p = 0.00064			

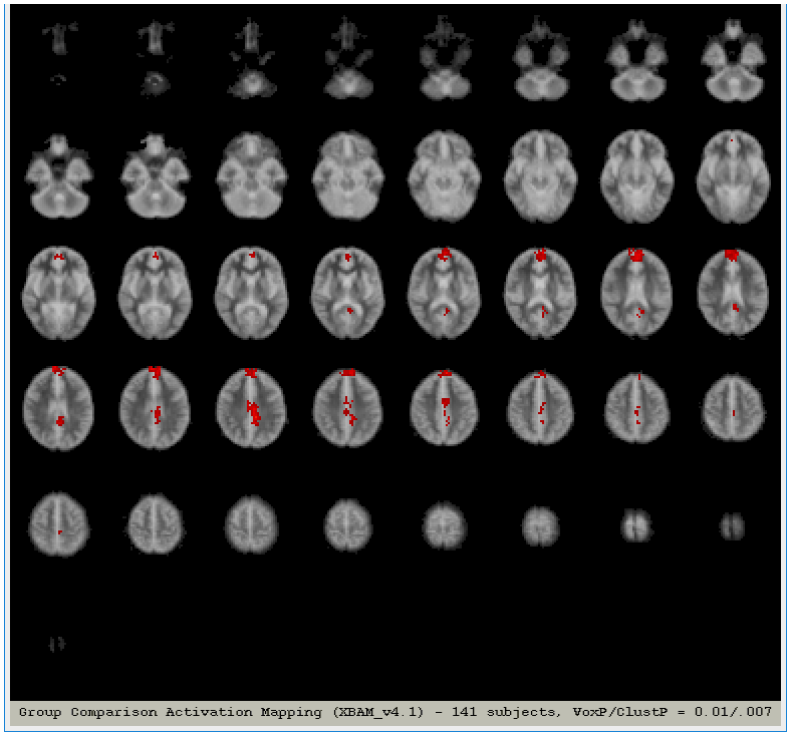
Figure Appx 3. 4 Haemodynamic response in the left Medial Frontal Gyrus (BA 8) at different levels of cognitive load in TRS individuals compared with Controls



	1-Back	2-Back	3-Back
TRS Group	-0.01912	-0.06601	-0.05857
Control Group	-0.04316	-0.15532	-0.17532
* Significant at p = 0.00128			

Figure Appx 3. 5 Statistical Maps in the factorial analysis (Cases vs Controls) at the voxel p-value threshold of 0.01





Factorial Analysis (Lower and Higher PANSS) using the voxel p-Value of 0.01

Table Appx. 3. 2 Factorial ANCOVAs comparing the haemodynamic response in the Lower and Higher PANSS Groups using a voxel p-Value of 0.01

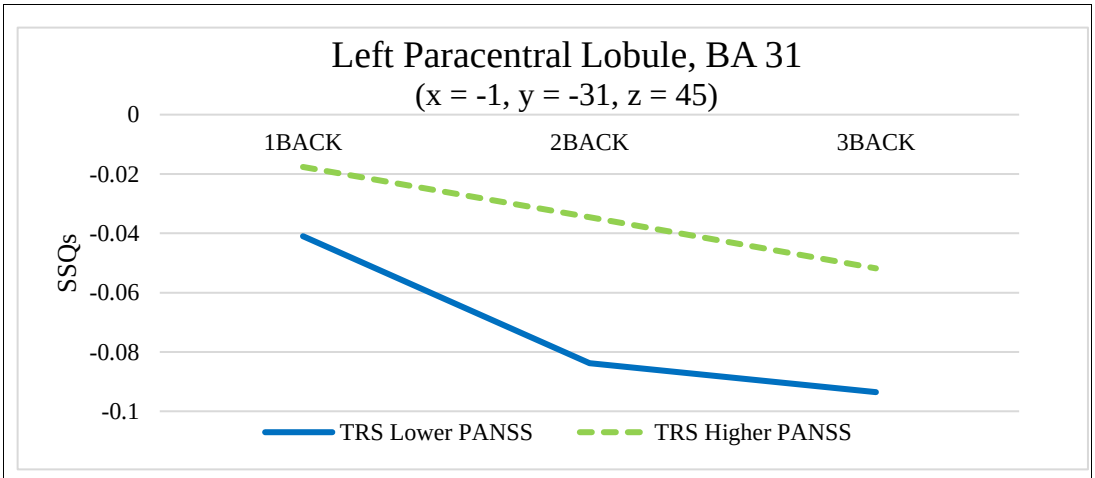
Anatomical Location	Brodmann Area	Hemis-phere	Cluster size (mm^3)	p-Value	Talairach co-ordinates*		
					x	y	z
Paracentral Lobule	BA 31	L	101	0.0016	0	-33	43

NB: Age was a covariate; threshold used voxel p value = 0.1

Anatomical Location	Brodmann Area	Hemis-phere	Cluster size (mm^3)	p-Value	Talairach co-ordinates*		
					x	y	z
Supramarginal Gyrus	BA 40	L	43	0.00342	-43	-48	33
Middle Frontal Gyrus	BA 9	L	65	0.00137	-36	26	30
Middle Frontal Gyrus	BA 6	R	34	0.00343	29	-4	50

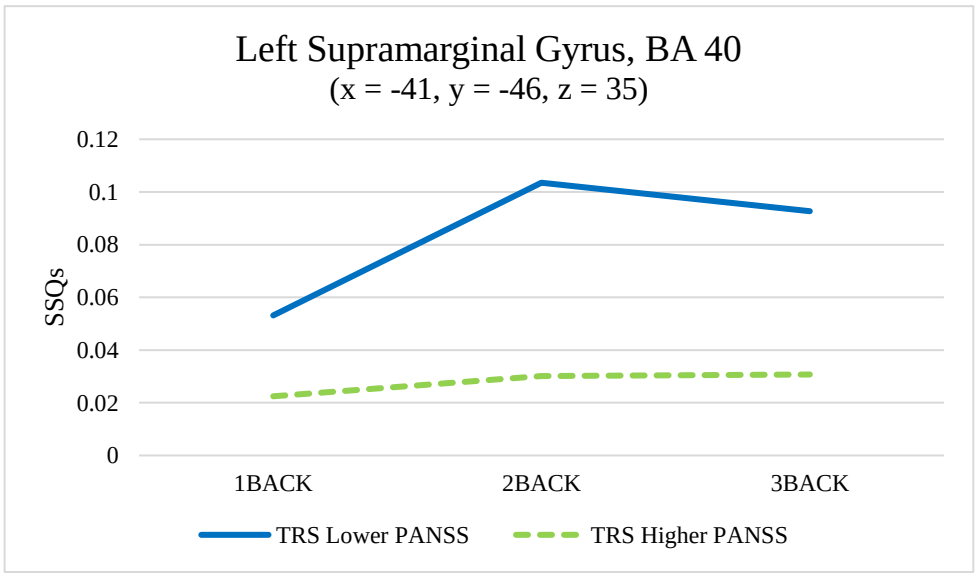
NB: Activation clusters ordered from anterior to posterior
Age was a covariate; threshold used voxel p value = 0.1

Figure Appx. 3. 6 Haemodynamic response in right Middle Frontal Gyrus (BA 6) at different levels of cognitive load in TRS individuals grouped by symptom severity



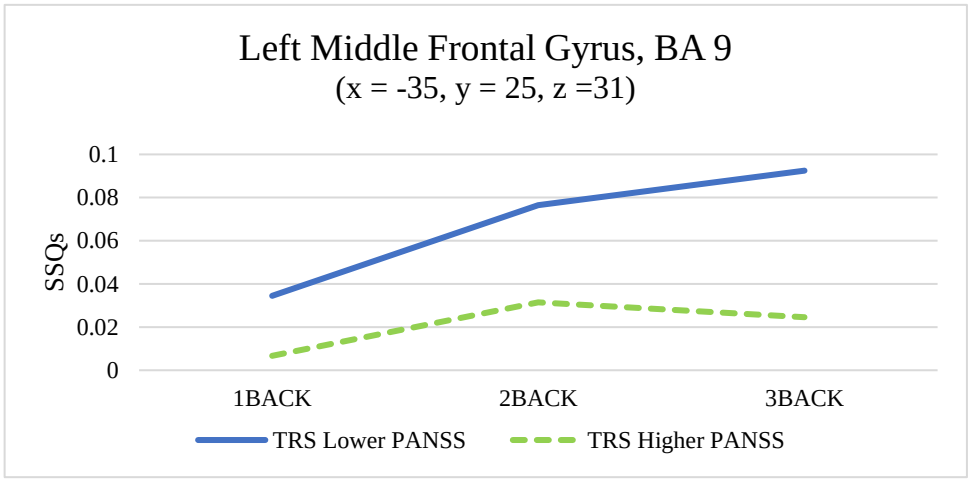
	1-Back	2-Back	3-Back
TRS Higher PANSS	-0.04098	-0.08382	-0.09355
TRS Lower PANSS	-0.01764	-0.03462	-0.05182
* Significant at p = 0.001552			

Figure Appx. 3. 7 Haemodynamic response in the left Supramarginal Gyrus (BA 40) at different levels of cognitive load in TRS individuals grouped by symptom severity



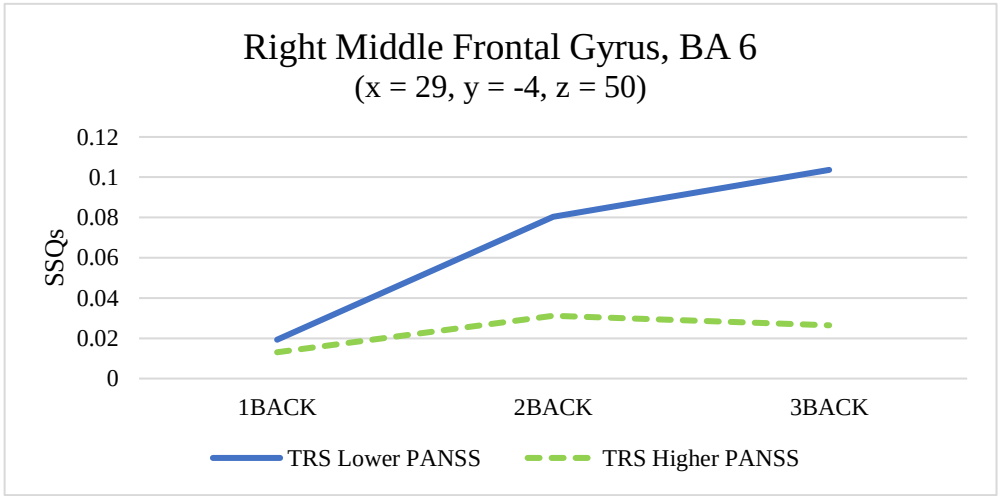
	1-Back	2-Back	3-Back
TRS Higher PANSS	0.05316	0.10351	0.09271
TRS Lower PANSS	0.02246	0.03015	0.03074
* Significant at p = 0.003428			

Figure Appx. 3. 8 Haemodynamic response in left Middle Frontal Gyrus (BA 9) at different levels of cognitive load in TRS individuals grouped by symptom severity



	1-Back	2-Back	3-Back
TRS Higher PANSS	0.03449	0.07644	0.09248
TRS Lower PANSS	0.00669	0.03146	0.02461
* Significant at p = 0.001371			

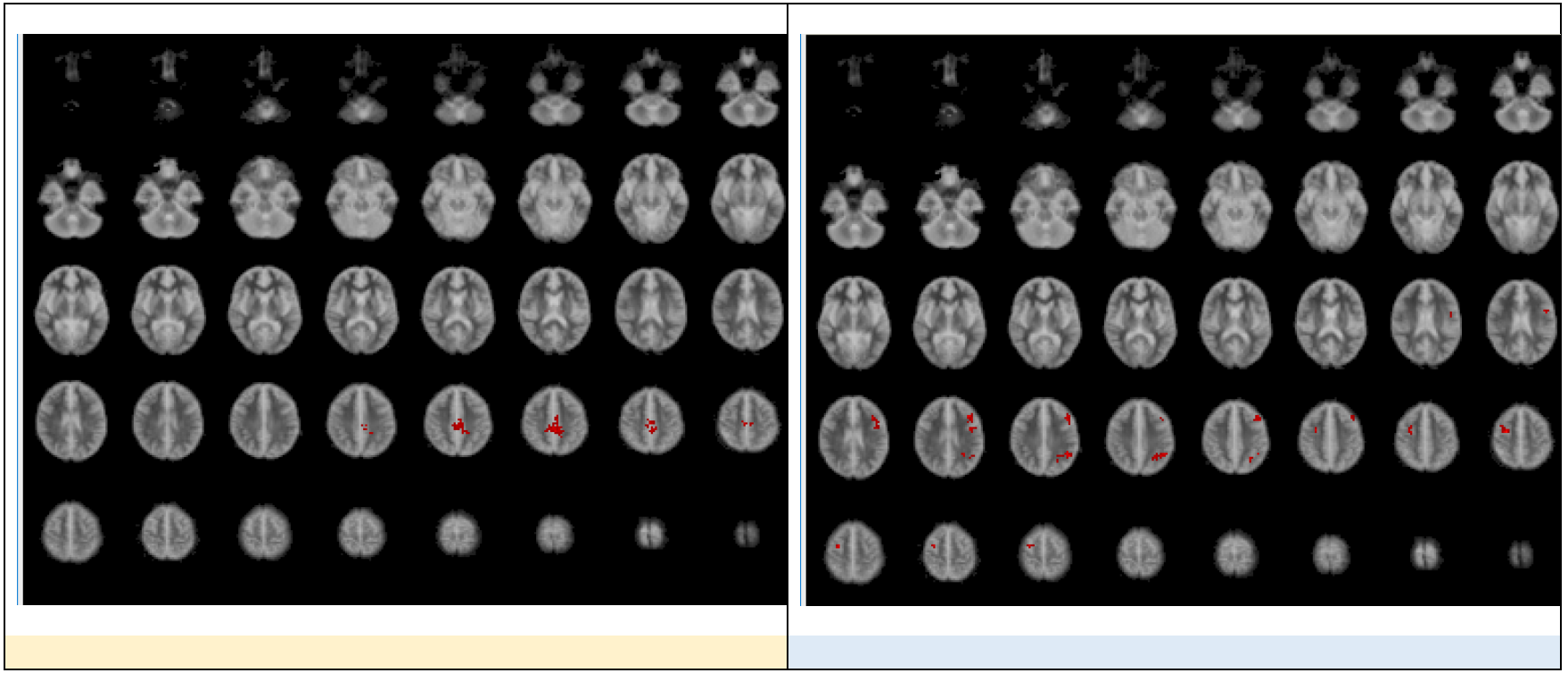
Figure Appx. 3. 9 Haemodynamic response in right Middle Frontal Gyrus (BA 6) at different levels of cognitive load in TRS individuals grouped by symptom severity



	1-Back	2-Back	3-Back
TRS Higher PANSS	0.01930	0.08033	0.10363
TRS Lower PANSS	0.01307	0.03119	0.02640
* Significant at p = 0.003428			

Figure Appx. 3. 10 Statistical Maps in the factorial analysis (Lower vs Higher PANSS) at the voxel p-value threshold of 0.01

Statistical Maps of the Factorial Interaction between TRS Participants Grouped According to Symptom Severity (Lower and Higher PANSS) and Cognitive Load using a threshold at voxel p value = 0.01



APPENDIX 4:

Supplementary Data - Verbal Learning using the HVLT-R

Table Appx. 4. 1 Attenuated Recency Effect in the Recall of Auditorily Presented Word Lists in TRS?

	1st Presentation	2nd Presentation	3rd Presentation
Lower PANSS	Number of items recalled at the last 3 positions in the list	Number of items recalled at the last 3 positions in the list	Number of items recalled at the last 3 positions in the list
ID09*	2	3 = recency effect?	3 = recency effect?
ID 10	2	2	2
ID 11	2	2	3 = recency effect?
ID 38*	2	2	3 = recency effect?
ID 13	2	1	2
ID 23	1	3 = recency effect?	2
ID 25	1	3 = recency effect?	3 = recency effect?
ID 14	1	2	2
ID 18	1	2	3 = recency effect?
ID 15	0	2	2
ID 17*	0	2	2
ID 24	0	2	2
ID 43	0	0	0
Higher PANSS			
ID 48**	3 = recency effect?	3 = recency effect?	3 = recency effect?
ID 08***	3 = recency effect?	2	3 = recency effect?
ID 22	2	2	2
ID 26	2	2	2
ID 15	1	2	2
ID 19	1	2	1
ID 45*	1	3 = recency effect?	3 = recency effect?
ID 46	1	3 = recency effect?	3 = recency effect?
ID 27	1	1	2
ID 41	0	0	2
ID 44	0	1	0
Mean recall at last 3 position	1.21	1.96	2.17
No. individuals who recalled all last 3 items, (% of group)	2 (8.3%)	6 (25%)	9 (42%)
No. individuals who recalled 2/3 last items, (% of group)	7 (29.2%)	13 (54.2%)	12 (50%)

N = 24

Behaviourally, it is noted that on the first trial:
Ninety-two percent (22/24) of TRS participants did not begin recall with the last item from the list.
* VIQ>PIQ individuals. Despite superior verbal IQ, none who showed this asymmetry started their recall on the first trial with any item from the last 3 positions in the list.
** The last three items were recalled at the end, in reverse order starting with "hut".
*** None achieved the classic pattern of starting recall with the last three items in reverse order, however, one participant started with the item at the 10th position, then the 11th and then the 12th.

Supplementary Data - Some Inter-correlations between the MCCB Scores and other Neuropsychological, Behavioural and Clinical Measures

The correlations in Table Appx. 4. 2 below are mostly between MCCB domains and the MCCB overall composite scores using the standardised percentile scores, except for total negative and positive symptom scores, also RTs and SDs in the 0-Back condition of the N-Back task (proposed as proxy measures of processing speed and sustained attention, respectively).

The correlations with the MCCB overall composite involving verbal and visual learning, PIQ and VIQ are also shown in Table 3. 11, section 3.5, but are repeated here so all the composite correlations are in one place and because the presence of p-values at .001 and .000 in the output are reflected in the .0005 value (the only place this occurs in this thesis).

Table Appx. 4. 2 Correlations with MCCB Domain and Composite Scores

	Spearman's Rho	Number in TRS Group	P- value
MCCB Speed of Processing Composite	TRS (PSZ)		
- MCCB Overall Composite	.750 ¬ .91	24	.0005***
- Symbol Coding (BAC SC)	.712	24	.0005***
- Trail Making Test (TMT)	.373	24	.073
- Category Fluency	.305	24	.147
- Reaction Times in the 0-Back Condition	-.405	24	.050*
MCCB Working Memory Composite			
- MCCB Overall Composite	.718 ¬ .83	24	.0005***
- Verbal Span	.633		.001***
- Spatial Span	.504	24	.012*
Learning correlated with the MCCB Overall Composite			
- Verbal Learning	.415 ¬ .8	24	.043*
- Visual Learning	.818 ¬ .79	24	.0005***
Attention correlated with the MCCB Overall Composite			
- Sustained Attention/Vigilance (CPT-IP)	.485 ¬ .86	24	.016*
- Standard Deviations in the 0-Back	-.373	24	.073
Reasoning and Problem Solving correlated with the MCCB Composite			
- NAB Mazes	.713 ¬ .64	24	.001***
Social Cognition			
- MCCB Overall Composite	.262 ¬ .65	24	.216
Estimated IQ (WASI) correlated with the MCCB Overall Composite			
- Full-Scale IQ	.681	24	.0005***
- Performance IQ	.689	24	.0005***
- Verbal IQ	.536	24	.007***
Symptoms (PANSS) correlated with the MCCB Overall Composite			
- Total Negative Symptoms Scores	-.455	23	.029*
- Total Positive Symptoms Scores	-.314	23	.144
- Total PANSS Score	-.493	24	.014*

Correlations based on percentile scores, apart from PANSS symptoms, 0-Back RTs and 0-Back SDs.
* = significant at p = .05; ** = significant at p = .01;
*** = significant after Bonferroni correction for family of 22 comparisons at p = .002.
P-values of .0005 used in this table to differentiate SPSS output of p = .000 from p = 001
¬ coefficient from study with 47 PSZ participants by Sui et al., 2015.

General Note: Cohen (1988), pp. 79-81 proposed the strength of a correlation coefficient is small if r = .10 to .29; medium if r = .3 to .49; large if r = .50 to 1.0.

Table Appx. 4. 3 Descriptive Statistics for Estimated IQ Scores in the TRS group

Mean Estimated IQ in the TRS Group (n=25)

	Full Scale IQ		Verbal IQ		Performance IQ	
Mean (SD)	101.68	(14.63)	100.24	(17.42)	102.28	(12.75)
N (Min-Max)	25	(61-124)	25	(55-130)	25	(70-127)
Mean (SD) of reduced set	100.00	(14.64)	96.00	(14.93)	103.33	(12.79)
N (Min-Max)	21	(61-124)	21	(55-120)	21	(70-127)

Median Estimated IQ in the TRS Group (n=25)

	Full Scale IQ		Verbal IQ		Performance IQ	
Median	104.00		99.00		105.00	
N (Interquartile range)	25	(92-111.5)	25	(89.5-110)	25	(94.5-105)
Median of reduced set	100.00		99.00		105.00	
N (Interquartile range)	21	(89-109.5)	21	(87-106)	21	(96-110.5)

Table Appx. 4. 4 Correlations involving Crystallised and Fluid Intelligence (VIQ and PIQ) with Performance on the MCCB by TRS Participants (full set)

		WM Composite	Verbal WM	Visuospatial WM	TMT	BAC SC	Verbal Fluency	NAB Mazes	HVLT-R	BVMT	Managing Emotions
Verbal IQ subscale	Pearson Correlation	.409*	.593***	.098	¬ .017	.154	.246	.276	578***	.449*	¬ .370
	Sig. (2-tailed)	.047	.002	.648	.937	.473	.247	.191	.003	.028	.075
	N	24	24	24	24	24	24	24	24	24	24
Performance IQ subscale	Pearson Correlation	.699***	688***	.475*	¬ - .312	.454*	.532**	.564**	.392	598***	.001
	Sig. (2-tailed)	.001	.001	.019	.138	.026	.007	.004	.058	.002	¬ .997
	N	24	24	24	24	24	24	24	24	24	24

¬ indicates Spearman's rho

** Correlation is significant at the 0.01 level.

* Correlation is significant at the 0.05 level.

*** Significant after Bonferroni correction for a family of 20 comparisons; adjusted alpha = .003

Table Appx. 4. 5 MCCB Associations with Estimated IQ in the Full and Reduced TRS Set (excluding VIQ>PIQ individuals)

		PIQ	PIQ (reduced set)	VIQ	VIQ (reduced set)	FIQ	FIQ (reduced set)
Trail Making Test (TMT-A)	Pearson Correlation	-.305	-.466*	.011	-.256	-.133	-.357
	Sig. (2-tailed)	.147	.039	.960	.276	.536	.122
	N	24	20	24	20	24	20
Symbol Coding (BAC SC)	Pearson Correlation	.454*	.525*	.154	.272	.308	.398
	Sig. (2-tailed)	.026	.018	.473	.247	.143	.082
	N	24	20	24	20	24	20
Verbal Learning (HVLT-R)	Pearson Correlation	.392	.459*	.578**	.442	.552**	.452*
	Sig. (2-tailed)	.058	.042	.003	.051	.005	.045
	N	24	20	24	20	24	20
Spatial Span (WMS-III)	Pearson Correlation	.475*	.451*	.098	.311	.298	.395
	Sig. (2-tailed)	.019	.046	.648	.182	.158	.085
	N	24	20	24	20	24	20
Letter Number Sequence (LNS)	Pearson Correlation	.688***	.651**	.593**	.782***	.721***	.740***
	Sig. (2-tailed)	.001	.002	.002	.001	.001	.001
	N	24	20	24	20	24	20
Reasoning and Problem Solving (NAB Mazes)	Pearson Correlation	.564**	.628**	.276	.440	.463*	.566**
	Sig. (2-tailed)	.004	.003	.191	.052	.023	.009
	N	24	20	24	20	24	20

* Correlation is significant at the 0.05 level.

Table continued on next page …….

** Correlation is significant at the 0.01 level.

Uncorrected for multiple comparisons. Colour coded to indicate general pattern: green indicates possible "trend" significance ($p < .09$), pale yellow * (significant at $p = .05$); intermediate yellow ** (significant at $p = .01$); deep yellow *** (significant at $p = .001$)

Table Appx. 4. 5 continued: MCCB Associations with Estimated IQ in the Full and Reduced TRS Set (excluding VIQ>PIQ individuals)

		PIQ	PIQ (reduced set)	VIQ	VIQ (reduced set)	FIQ	FIQ (reduced set)
Visual Learning (BVMT-R)	Pearson Correlation	.598**	.585**	.449*	.418	.586**	.511*
	Sig. (2-tailed)	.002	.007	.028	.066	.003	.021
	N	24	20	24	20	24	20
Category Fluency (animal names)	Pearson Correlation	.532**	.609**	.246	.474*	.395	.529*
	Sig. (2-tailed)	.007	.004	.247	.035	.056	.016
	N	24	20	24	20	24	20
Social Cognition (MSCEIT ME)	Pearson Correlation	.148	.277	.408*	.445*	.340	.404
	Sig. (2-tailed)	.489	.238	.048	.050	.104	.077
	N	24	20	24	20	24	20
Sustained Attention/ Vigilance (CPT-IP)	Pearson Correlation	.315	.586**	.546**	.497*	.543**	.578**
	Sig. (2-tailed)	.143	.008	.007	.031	.007	.009
	N	23	19	23	19	23	19
Speed of Processing Composite (TMT+BACS+Fluency)	Pearson Correlation	.243	.240	.206	.177	.242	.207
	Sig. (2-tailed)	.252	.308	.333	.454	.254	.381
	N	24	20	24	20	24	20
Working Memory Composite (LNS+WMS-III)	Pearson Correlation	.699**	.649**	.409*	.634**	.608**	.664**
	Sig. (2-tailed)	.000	.002	.047	.003	.002	.001
	N	24	20	24	20	24	20

* Correlation is significant at the 0.05 level. ** Correlation is significant at the 0.01 level.

Note: The speed of processing composite was normally distributed, although the component TMT test was positively skewed.

Uncorrected for multiple comparisons. Colour coded to indicate general pattern: green indicates possible "trend" significance ($p < .09$), pale yellow * (significant at $p = .05$); deep yellow ** (significant at $p = .01$).

Table Appx. 4. 6 Correlations between Symptom Scores and MCCB Test Performances

Spearman's Rho		PANSS Total	PANSS Total (Reduced set)	Negative Symptoms	Negative Symptoms (Reduced set)
Trail Making Test (TMT-A)	Coefficient	.263	.362	.024	.114
	Significance	.215	.117	.912	.643
	N	24	20	23	19
Symbol Coding (BAC SC)	Coefficient	-.231	-.289	-.129	-.194
	Significance.	.278	.216	.557	.427
	N	24	20	23	19
Verbal Learning (HVLT-R)	Coefficient	.058	.133	-.135	.001
	Significance	.786	.576	.540	.997
	N	24	20	23	19
Spatial Span (WMS-III)	Coefficient	-.145	-.307	.121	-.044
	Significance	.499	.188	.581	.858
	N	24	20	23	19
Letter Number Sequence (LNS)	Coefficient	-.274	-.295	-.258	-.331
	Significance	.194	.207	.235	.167
	N	24	20	23	19
Reasoning and Problem Solving (NAB Mazes)	Coefficient	-.263	-.282	-.147	-.157
	Significance	.215	.228	.504	.521
	N	24	20	23	19
Visual Learning (BVMT-R)	Coefficient	-.346	-.378	-.296	-.344
	Significance	.097	.101	.171	.150
	N	24	20	23	19
Category Fluency	Coefficient	-.077	.103	-.072	.015
	Significance	.721	.664	.744	.950
	N	24	20	23	19
Social Cognition (MSCEIT ME)	Coefficient	-.172	-.152	-.354	-.275
	Significance	.422	.523	.098	.255
	N	24	20	23	19
Sustained Attention/ Vigilance (CPT-IP)	Coefficient	-.477*	-.311	-.564**	-.364
	Significance	.021	.196	.006	.137
	N	23	19	22	18
Speed of Processing (TMT+BACS+Fluency)	Coefficient	.188	.256	.101	.109
	Significance	.379	.275	.648	.657
	N	24	20	23	19
Working Memory (LNS+SpSp)	Coefficient	-.332	-.426	-.122	-.244
	Significance	.114	.061	.580	.314
	N	24	20	23	19

* Correlation is significant at the 0.05 level.

** Correlation is significant at the 0.01 level.

Uncorrected for multiple comparisons.

Table Appx. 4. 7 (a) Correlations concerning Time to access Clozapine and Duration of Treatment with Clozapine

			Time to access clozapine	Time on clozapine
Spearman's rho	Time between diagnosis and clozapine	Correlation Coefficient	1.000	
		Sig. (2-tailed)	.	
		N	25	
	Time on clozapine	Correlation Coefficient	-.403*	1.000
		Sig. (2-tailed)	.046	.
		N	25	25
	PANSS Score	Correlation Coefficient	.242	-.319
		Sig. (2-tailed)	.244	.120
		N	25	25
	Negative Symptoms	Correlation Coefficient	.242	-.293
		Sig. (2-tailed)	.255	.165
		N	24	24
	Zero-Back RTs	Correlation Coefficient	.145	.039
		Sig. (2-tailed)	.488	.852
		N	25	25
	Zero-Back SDs	Correlation Coefficient	.192	-.129
		Sig. (2-tailed)	.358	.539
		N	25	25
	Percentage of Omission Errors (to 36 targets across all conditions in the n-back)	Correlation Coefficient	.068	-.082
		Sig. (2-tailed)	.746	.697
		N	25	25
	Category Fluency (animal names)	Correlation Coefficient	-.089	¬ .272
		Sig. (2-tailed)	.687	.209
		N	23	23
	Sustained Attention/ Vigilance (CPT-IP)	Correlation Coefficient	-.289	¬ -.115
		Sig. (2-tailed)	.191	.610
		N	22	22

Table continues on next page .....

¬ indicates Pearson Product Moment Coefficient

* Correlation is significant at the 0.05 level.

** Correlation is significant at the 0.01 level.

After Bonferroni correction for a family of 30 comparisons adjusted alpha = .002

Table Appx. 4. 7 continued (b) Correlations concerning Time to access Clozapine and Duration of Treatment with Clozapine

			Time to access clozapine	Time on clozapine
Spearman's rho	Time between diagnosis and clozapine	Correlation Coefficient	1.000	¬ -.397*
		Sig. (2-tailed)	.	.049
		N	25	25
	Time on clozapine	Correlation Coefficient	¬ -.397*	1.000
		Sig. (2-tailed)	.049	.
		N	25	25
	Recall on first trial of HVLT-R	Correlation Coefficient	¬ -.474*	¬ .419*
		Sig. (2-tailed)	.022	.047
		N	23	23
	Verbal Learning/ STM HVLT-R	Correlation Coefficient	¬ -.438*	¬ .382
		Sig. (2-tailed)	.037	.072
		N	23	23
	Visual Learning BVMT	Correlation Coefficient	¬ -.521*	¬ .225
		Sig. (2-tailed)	.011	.302
		N	23	23
	Full Scale IQ	Correlation Coefficient	¬ -.234	¬ .184
		Sig. (2-tailed)	.271	.389
		N	24	24
	Verbal IQ	Correlation Coefficient	¬ -.207	¬ .147
		Sig. (2-tailed)	.333	.492
		N	24	24
	Performance IQ subscale	Correlation Coefficient	¬ -.209	¬ .201
		Sig. (2-tailed)	.327	.347
		N	24	24
	MCCB Overall Composite Score (percentiles)	Correlation Coefficient	-.549**	.281
		Sig. (2-tailed)	.007	.195
		N	23	23

¬ indicates Pearson Product Moment Coefficient
* Correlation is significant at the 0.05 level.
** Correlation is significant at the 0.01 level.
After Bonferroni correction for a family of 30 comparisons adjusted alpha = .002

It is noted there was a significant negative correlation between time to access clozapine and the duration of treatment with clozapine, indicating that the longer the wait, the shorter the duration of treatment. None of the other correlations with duration of treatment with clozapine were significant.

Comparison of TRS Domain Profiles with other Studies of Schizophrenia (not identified as TRS)

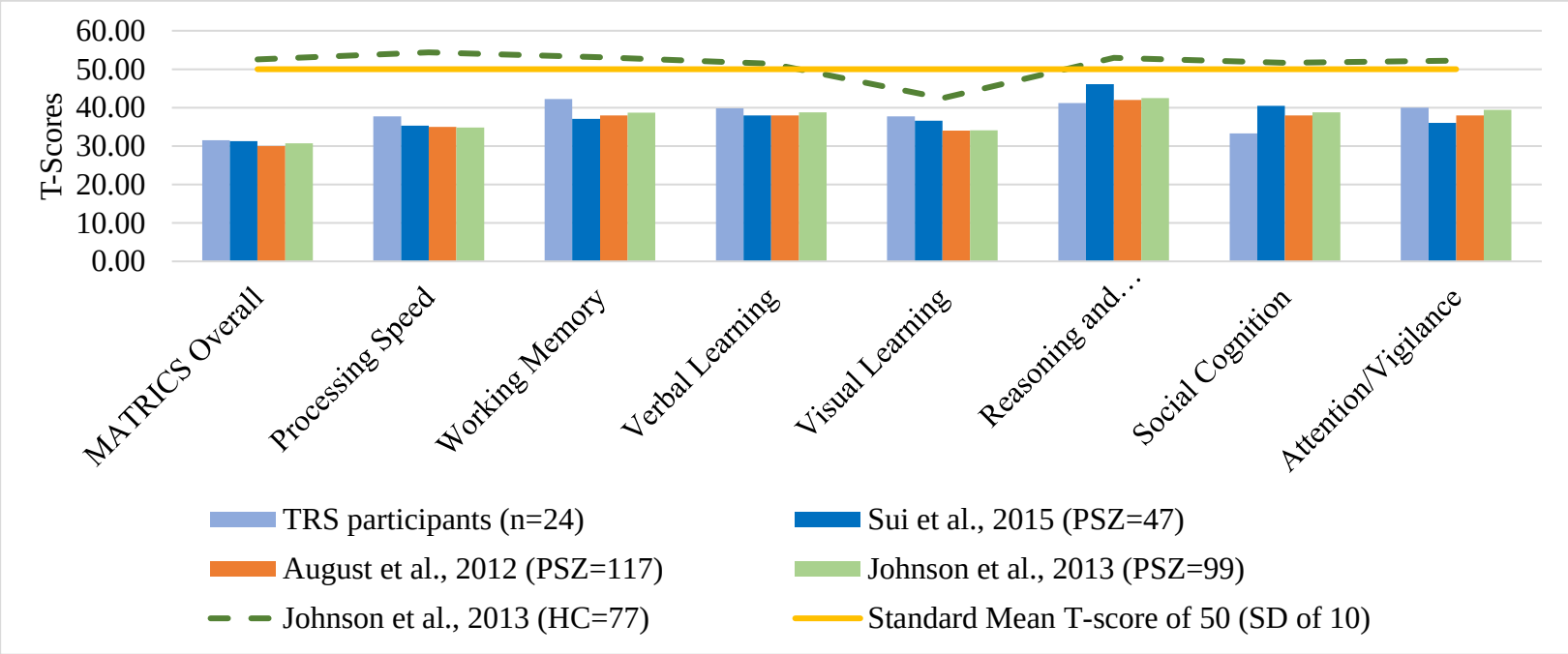
These were conducted out of curiosity in case of clear disparity with the TRS group, but the main inference is to be beware of perceived similarities. However, the scores for the control group in Johnson et al. (2017) around the 50th percentile in Figure Appx. 4. 1 support the standardisation study.

Table Appx. 4. 8 Descriptive Comparison of MCCB Domain Profile T-Scores with other Studies*

	This Study TRS (n=24)	Sui et al., 2015 (PSZ=47)	August et al., 2012 (PSZ=117)	Johnson et al., 2013 (PSZ=99)	Johnson et al., 2013 (HC=77)
MCCB Overall Composite	31.52	31.3	30	30.7	52.55
Processing Speed	37.71	35.3	35	34.85	54.38
Working Memory	42.25	37.1	38	38.67	53.14
Verbal Learning	39.79	38	38	38.81	51.42
Visual Learning	37.75	36.6	34	34.1	42.46
Reasoning and Problem Solving	41.17	46.1	42	42.46	52.95
Social Cognition	33.29	40.5	38	38.76	51.68
Attention/Vigilance	40.00	36	38	39.43	52.25

PSZ = participants with schizophrenia (not identified as TRS).
HC = healthy controls.
* Note: Based on published T-scores, this data is also depicted in Figure Appx. 4. 1

Figure Appx. 4. 1 Comparison of MCCB Domain Profiles with other Studies



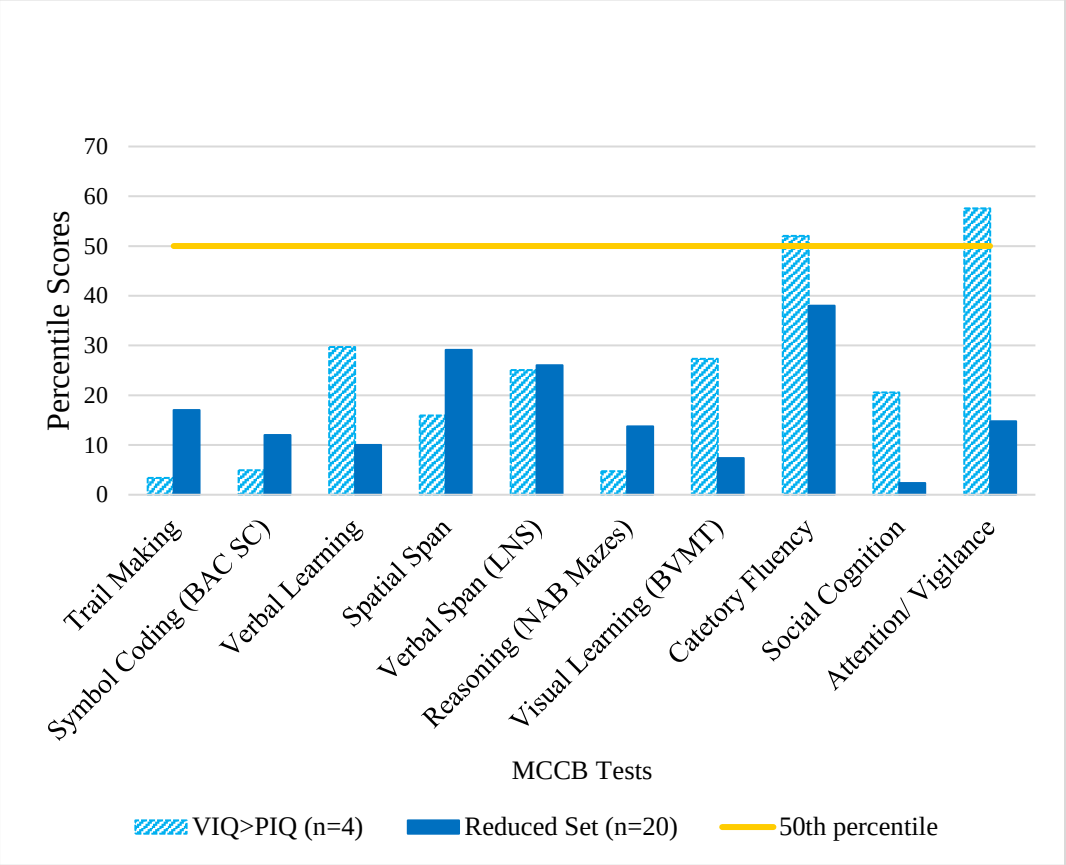
PSZ = participants with schizophrenia. HC = healthy control participants (the T-score at 50 also represents the 50th percentile of the standardisation study by Kern et al., 2011).

Note: all the published studies were conducted in the USA.

APPENDIX 5:

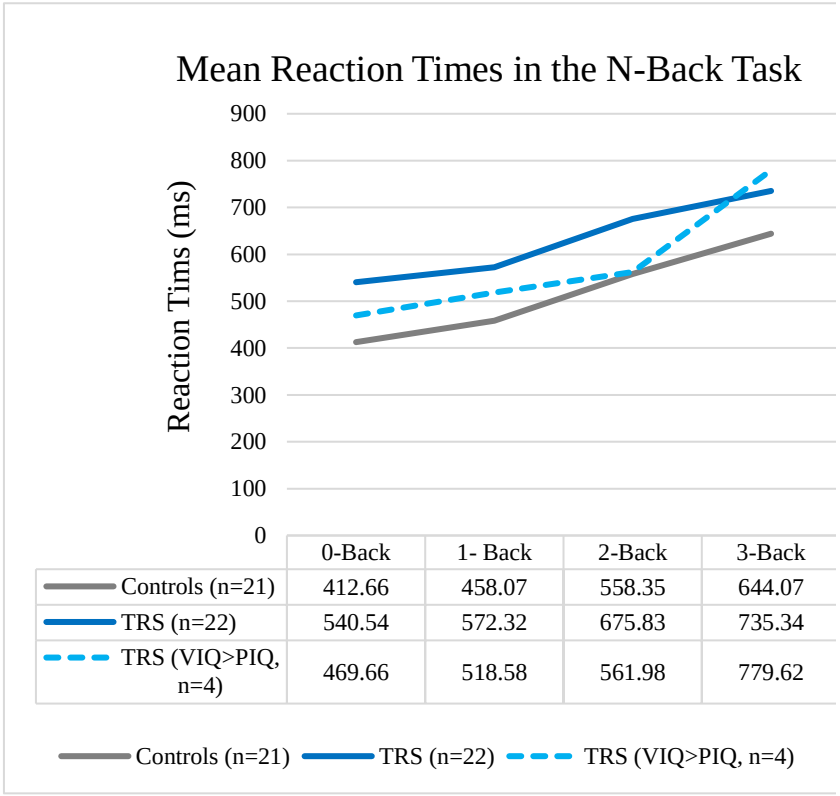
Descriptive characterisation of the superior VIQ grouping (VIQ>PIQ), n=4

Figure Appx. 5. 1 Comparison of Median Scores on the MCCB in the Superior VIQ and Reduced TRS Groupings

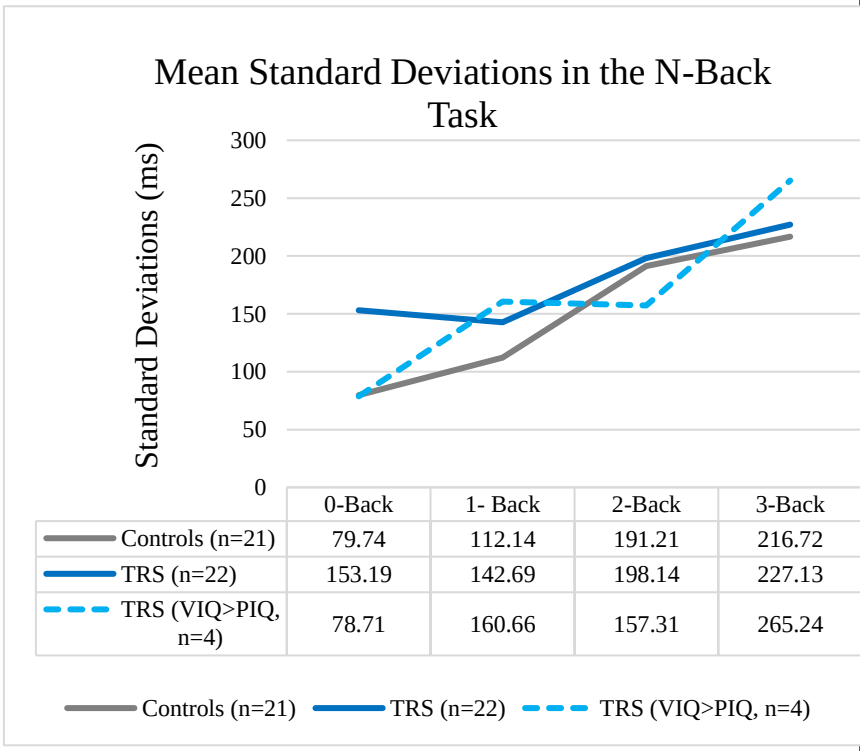


MCCB Tests	TRS (VIQ>PIQ) n =4		TRS Reduced Set, n=22	
	Median Percentile	Interquartile range	Median Percentile	Interquartile range
Trail Making Test (TMT-A)	3.4	0.1 - 19.7	17.0	5.1 - 34
Symbol Coding (BACS SC)	4.95	2.5 - 17.7	12.0	2.7 - 48
Verbal Learning (HVLT-R)	29.7	11.3 - 66.6	10.0	5.5 - 25.5
Spatial Span (WMS-III)	15.95	6.2 - 29.8	29.1	18 - 68.3
Letter-Number Span (LNS)	25.05	4.7 - 62.3	26.0	16.5 - 41.1
Reasoning and Problem Solving (NAB Mazes)	4.75	1.4 - 47.6	13.8	8.5 - 26.3
Visual learning (BVMT-R)	27.3	0.4 - 85.8	7.4	1.4 - 37
Category Fluency	52	12.9 - 71	38.0	19.5 - 64.6
Social Cognition (MSCEIT ME)	20.6	0.8 - 68.7	2.4	0.4 - 4.3
Attention and Vigilance (CPT-IP)	57.6	32.1 - 72	14.8	3.7 -21.2

Figure Appx. 5. 2 Descriptive data for mean reaction times and standard deviations in the reduced set of TRS participants, the superior VIQ asymmetry grouping and the control group



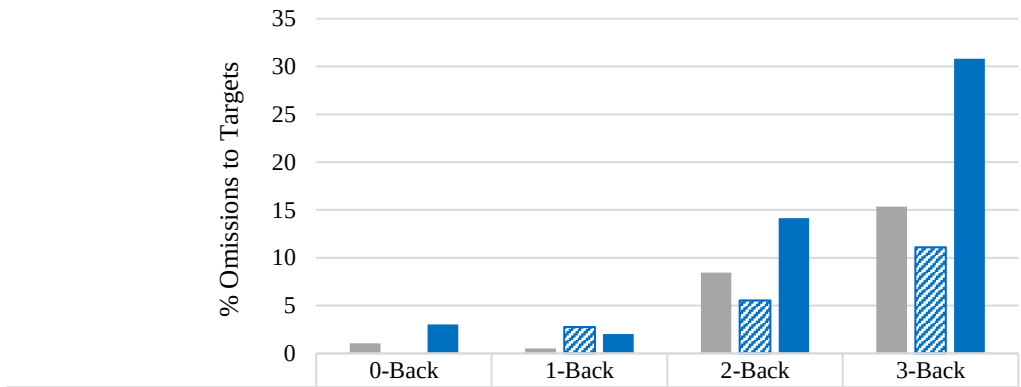
	0-Back	1- Back	2-Back	3-Back
Controls (n=21)	412.66	458.07	558.35	644.07
TRS (n=22)	540.54	572.32	675.83	735.34
TRS (VIQ>PIQ, n=4)	469.66	518.58	561.98	779.62



	0-Back	1- Back	2-Back	3-Back
Controls (n=21)	79.74	112.14	191.21	216.72
TRS (n=22)	153.19	142.69	198.14	227.13
TRS (VIQ>PIQ, n=4)	78.71	160.66	157.31	265.24

Note: Full descriptive data available in Table Appx. 5. 3

Figure Appx. 5. 3 Descriptive data for omission errors in the reduced set of TRS participants, superior VIQ asymmetry grouping and control group



	0-Back	1-Back	2-Back	3-Back
Control Group, n=21	1.06	0.53	8.46	15.34
Superior VIQ (VIQ>PIQ), n=4	0.00	2.78	5.55	11.11
Reduced set of TRS, n=22	3.03	2.02	14.14	30.81

The four VIQ>PIQ participants were distinguished in various ways, as above. As summarised in Table 3. 20, these included a higher median estimated FIQ standard score (at 111.5, compared with 103 in the 'no asymmetry' group and 99 in the 'superior PIQ' group); a low level of negative and positive symptoms (although one participant was classified as "higher PANSS" on the basis of their scores on the general scale). Visual inspection of median percentile scores on the MCCB tests (adjusted for age and gender) depicted in Figure Appx. 5. 1, indicated that their scores were markedly depressed compared to the standardisation norm represented at the 50th percentile, with the exception of category fluency and scores on the measure of sustained attention/vigilance (CPT-IP) which surpassed the reduced set of TRS participants, indeed, passed the 50th percentile. Moreover, as can be seen in descriptive data of differences in mean RTs and SDs shown in Table Appx. 5.3, the mean of 0-Back SDs was virtually identical to that of the control group, and almost half that of the reduced set of 20 TRS participants, thereby, possibly providing some convergent support for superior CPT-IP scores in Figure Appx. 5.1.

Reaction times in the 0-Back condition in the VIQ>PIQ group were intermediate - between those of the control group and the other TRS participants. Figure Appx. 5. 2 depicts this data for every condition, where it can be seen performance of the VIQ>PIQ grouping slowed remarkably at the highest level of cognitive load. This could be related to the increase in omission errors during the 3-Back condition by the VIQ>PIQ group, depicted in Figure Appx. 5. 3. One possible explanation is that these participants were better able to detect their errors and tried to adjust their responses following error detection (e.g. a

speed/accuracy trade-off), thereby exhibiting post error slowing. This might also indicate a relative sparing of the monitoring function and use of prediction error, which is associated with the ACC. By contrast, RTs in the rest of the TRS group did not increase as much as might have been expected given the higher rate of errors in the 3-Back condition. Indeed, they might have been expected to diverge with the control group which had a lower error rate (Figure Appx. 5. 2) by responding more cautiously after making errors. However, the pattern is consistent with the faulty use of prediction error and a failure to notice or, perhaps, act on errors by the main TRS group.

Explorations with a reduced dataset (without the VIQ>PIQ grouping)

Correlational analyses with the reduced data set, n=18-22

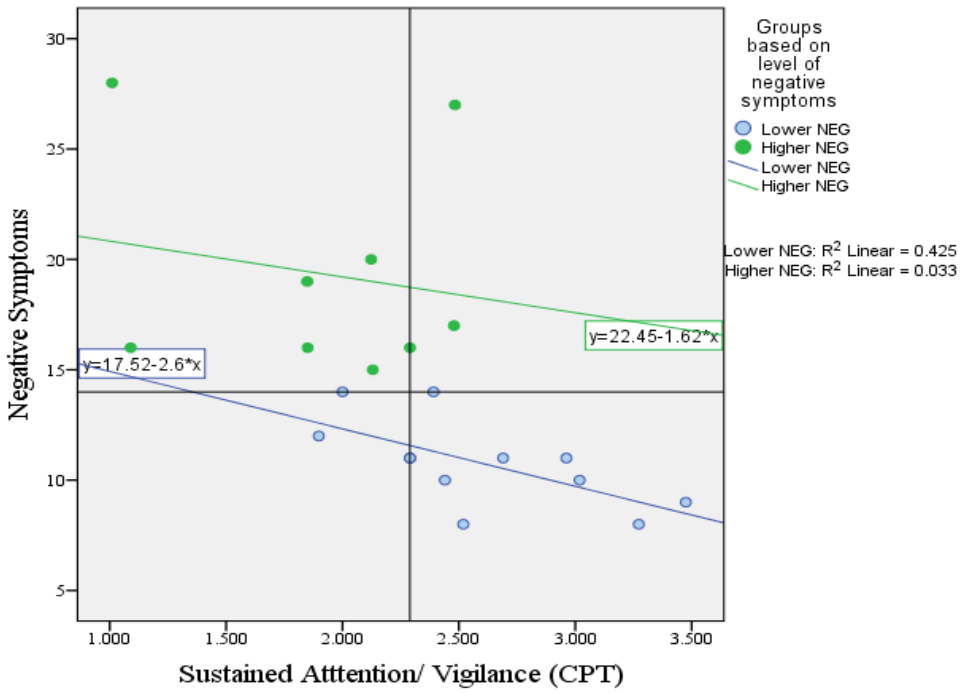
The exclusion of data from participants on the basis they might be outliers in some way, increases the risk of losing aspects of data which may be important to interpretation. However, in the case of asymmetries between the WASI subscales, 48% exhibited little or no asymmetry, while there were two polarised populations exhibiting sizeable asymmetries which behaved differently in other respects as summarised above. In the scatterplots of correlations between WASI Asymmetry and CPT-IP scores, also 0-Back SDs (Figure Appx. 5. 5) the four VIQ>PIQ participants are identifiable on the positive side of the horizontal axis forming clusters (loosely in the plot with CPT-IP scores and more closely in the plot for 0-Back SDs). Therefore, some of the correlations in Table 3. 17 and 3.18 were repeated without the four VIQ>PIQ participants. These are shown in Appendix 5 (Table Appx. 5. 1 and Table Appx. 5. 2).

Briefly, the analyses confirmed these participants had had a polarising effect in some correlations: their removal abolished the highly significant correlation between negative symptoms and performance on the CPT-IP (rho = -.364, n=18, p = .137), which was not unexpected as the four (VIQ>PIQ) participants had a low level of negative symptoms and relatively good scores on the CPT-IP. Also, the correlation between negative symptoms and omission errors on the n-Back task was no longer significant (rho = .096, n= 21, p = .096). While the correlation between CPT-IP scores and omission errors (previously at trend significance, p = 0.063) remained nonsignificant (rho = .308, p = .199, n=19). However, the correlation between negative symptoms and mean standard deviations in the 0-Back condition remained highly significant (rho = .750, n=21, p = .001) and would survive Bonferroni correction in a family of 24 comparisons. Further, the correlation of medium strength between mean standard deviations in the 0-Back task and CPT-IP scores remained significant and was slightly stronger in the reduced set (rho = -.484, n=19, p = .036).

Moreover, the correlation between mean standard deviations in the 0-Back condition and the percentage of omission errors in the n-Back task was now significant (rho = .473, p = .026, n=22).

The survival of the correlation between negative symptoms and mean standard deviations in the 0-Back conditions merits further consideration and as previously suggested, the CPT-IP might make notable demands upon selective attention as well as sustained attention. This could help to account for the latter's nonsignificant correlation with negative symptoms. However, inspection of the scatterplot for the now non-significant correlation (not depicted) revealed the influence of a single outlier where a participant had a high level of negative symptoms but also performed well on the CPT-IP task. Also, they were not typical with superior estimated IQ scores (FIQ =121, PIQ = 127, VIQ = 111). Uniquely for this study, the correlation was repeated without the scores of the participant which resulted in a significant correlation shown in Figure Appx. 5. 4 below. Arguably, this restores the relationship between negative symptoms and CPT-IP scores observed in the full TRS set (Table 3. 17). Collectively, this set of observations indicates that even in the reduced set, negative symptoms were associated with attentional variables.

Figure Appx. 5. 4 Correlation between Negative Symptoms and Performance on the CPT-IP task in a reduced set of TRS participants*



* Correlation excluded 4 participants showing a marked asymmetry between WASI subscales (VIQ>PIQ). This correlation also excluded an outlier exhibiting a high level of negative symptoms but superior performance on the CPT-IP: rho = -.536, n=17, p = .026.

Correlations with a Reduced Set of TRS Participants (excluding VIQ>PIQ)

This section contains tables of correlations between neuropsychological and behavioural variables based on a reduced set of participants after the removal of small subset of participants with an asymmetry between WASI subscales that favoured the VIQ. They also had markedly higher estimated FIQ scores than the other participants along with very low level of negative symptoms. As such they might represent a confound in the data.

Table Appx. 5. 1 Inter-correlations between Variables Proposed to be Associated with Attention in a reduced set of 20 TRS participants excluding those with superior VIQ relative to PIQ (VIQ>PIQ)

Spearman's rho:		Negative Symptoms	Standard Deviations in 0-Back Condition	Continuous Performance Task (CPT-IP)	Percentage of Omission Errors (N-Back task)
Negative Symptoms	Correlation Coefficient	1.000			
	Sig. (2-tailed)	.			
	N	21			
Standard Deviations in 0-Back Condition	Correlation Coefficient	.750**	1.000		
	Sig. (2-tailed)	001	.		
	N	21	21		
Continuous Performance Task (CPT-IP)	Correlation Coefficient	¬-.364	-.484*	1.000	
	Sig. (2-tailed)	.137	.036	.	
	N	18	19	19	
Percentage of Omission Errors in the N-Back task (to 36 targets)	Correlation Coefficient	.373	.473*	-.308	1.000
	Sig. (2-tailed)	.096	026	.199	.
	N	21	22	19	22

* Correlation is significant at the 0.05 level.
** Correlation is significant at the 0.001 level.
Bonferroni correction for 24 comparisons sets alpha at .002, Tables Appx. 5.1, Appx. 5.2.

¬ Correlation became significant again, once the influence of an outlier was removed from the computation, as described in Figure Appx 5. 4 above.

Note: See Table 3. 17 for the correlations with the full set of TRS participants.

Table Appx. 5. 2 Correlations between Variables associated with Attention and WASI Scores including Subscale Asymmetry in a reduced set of TRS participants (excluding those with superior VIQ scores relative to PIQ (VIQ>PIQ)

Spearman's rho (except where ¬ indicates Pearson).		Negative Symptoms	Standard Deviations in 0-Back Condition	Continuous Performance Task	Full-scale IQ	Verbal IQ	Performance IQ	Asymmetry between IQ subscales
Full-scale IQ	Correlation Coefficient	-.385	-.537*	.578**¬	1.000			
	Sig. (2-tailed)	.093	.012	.009	.			
	N	20	21	19	25			
Verbal IQ	Correlation Coefficient	-.375	-.531*	.497*¬	.964**¬	1.000		
	Sig. (2-tailed)	.103	.013	.031	.000	.		
	N	20	21	19	21	25		
Performance IQ subscale	Correlation Coefficient	-.294	-.464*	.586**¬	.945**¬	.830**¬	1.000	
	Sig. (2-tailed)	.208	.034	.008	.001	.001	.	
	N	20	21	19	21	21	25	
IQ Asymmetry	Correlation Coefficient	-.349	-.384	-.085	.187	.374	-.135	1.000
	Sig. (2-tailed)	.132	.085	.730	.417	.095	.559	.
	N	20	21	19	21	21	21	25

* Correlation is significant at the 0.05 level. ** Correlation is significant at the 0.01 level.

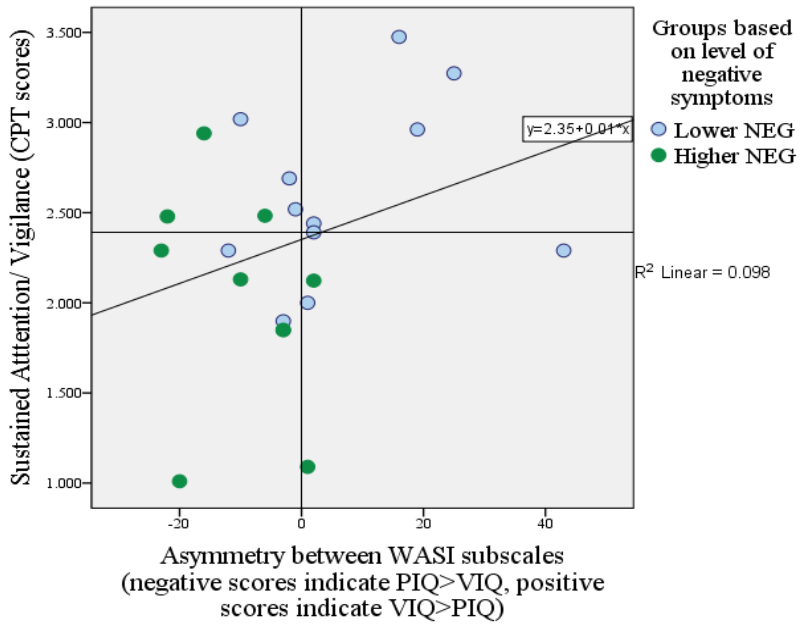
*** would survive Bonferroni correction with an alpha = .0021 for 24 comparisons (in Tables Appx. 5.1, Appx. 5.2).

¬ indicates use of the Pearson product moment correlation

Note: see Table 3. 18 for the corresponding analyses with the full dataset.

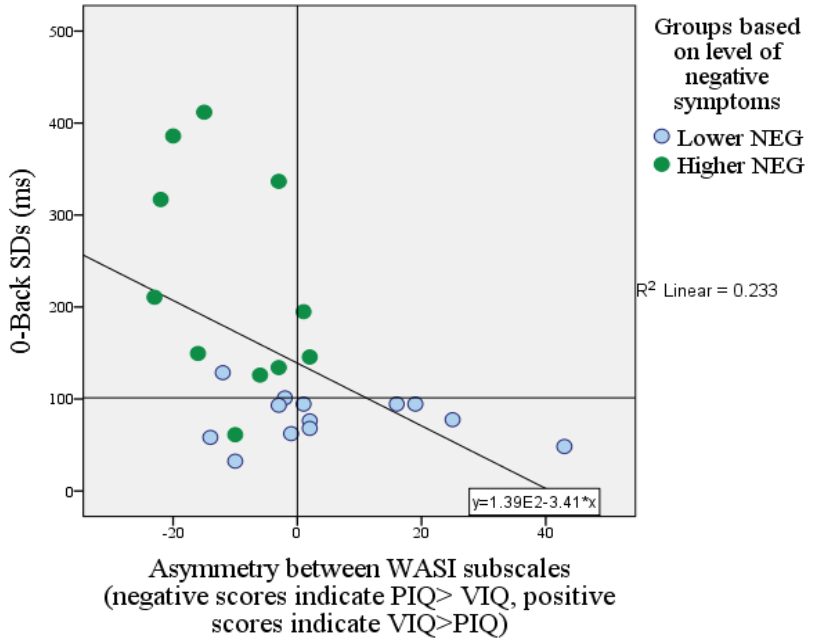
Figure Appx. 5. 5 Correlations involving Asymmetry between WASI subscales and Proposed Markers of Attention

a) Correlation between CPT-IP scores and IQ Asymmetry



Horizontal line indicates mean CPT-IP score at 2.34.
rho = -.276, n=23, p = .237

b) Correlation between 0-Back SDs and IQ Asymmetry



Horizontal line indicates median of 0-Back SDs scores at 101.21ms.
rho = -.450, n=25, p = .024

Note: in both of these plots the four data points on the right side represent individuals in the superior VIQ group.

Table Appx. 5. 3 Descriptive Statistics for Mean Reaction Times and Standard Deviations at Different Levels of Cognitive Load in the Control Group, Superior VIQ (VIQ>PIQ) Group, and the Reduced Set of TRS Participants

Control participants	N	Minimum	Maximum	Mean	Std. Deviation
Reaction Times					
ZeroBackRTs	21	297.78	630.11	412.66	83.04
OneBackRTs	21	340.22	638.22	458.07	89.93
TwoBackRTs	21	402.56	760.86	558.35	105.65
ThreeBackRTs	21	361.63	1067.83	644.07	159.10
Standard Deviations					
ZeroBackSDs	21	22.20	455.44	79.74	91.20
OneBackSDs	21	22.23	386.19	112.14	87.69
TwoBackSDs	21	85.66	384.63	191.21	88.67
ThreeBackSDs	21	69.76	448.54	216.72	105.92
Superior VIQ (VIQ>PIQ) participants	N	Minimum	Maximum	Mean	Std. Deviation
Reaction Times					
ZeroBackRTs	4	371.78	525.00	469.66	68.32
OneBackRTs	4	430.11	570.67	518.58	65.77
TwoBackRTs	4	461.78	668.22	561.98	84.38
ThreeBackRTs	4	673.86	845.33	779.62	74.32
Standard Deviations					
ZeroBackSDs	4	48.33	94.51	78.71	21.78
OneBackSDs	4	84.65	229.74	160.66	62.12
TwoBackSDs	4	88.54	201.27	157.31	54.52
ThreeBackSDs	4	117.46	374.54	265.24	108.78
Reduced set of TRS participants	N	Minimum	Maximum	Mean	Std. Deviation
Reaction Times					
ZeroBackRTs	22	370.56	851.38	540.54	132.73
OneBackRTs	22	372.78	912.00	572.32	137.90
TwoBackRTs	22	378.67	1204.63	675.83	203.35
ThreeBackRTs	21	332	1180	735.34	215.20
Standard Deviations					
ZeroBackSDs	22	32.38	411.82	153.19	111.20
OneBackSDs	22	27.04	274.34	142.68	64.16
TwoBackSDs	22	56.10	403.59	198.14	98.15
ThreeBackSDs	21	56.09	436.85	227.13	103.14

Table Appx. 5. 4 Associations between MCCB performance and Estimated IQ in the Full and Reduced TRS Sets

		PIQ	PIQ (reduced set)	VIQ	VIQ (reduced set)	FIQ	FIQ (reduced set)
Trail Making Test (TMT-A)	Pearson Correlation	-.305	-.466*	.011	-.256	-.133	-.357
	Sig. (2-tailed)	.147	.039	.960	.276	.536	.122
	N	24	20	24	20	24	20
Symbol Coding (BAC SC)	Pearson Correlation	.454*	.525*	.154	.272	.308	.398
	Sig. (2-tailed)	.026	.018	.473	.247	.143	.082
	N	24	20	24	20	24	20
Verbal Learning (HVLT-R)	Pearson Correlation	.392	.459*	.578***	.442	.552***	.452*
	Sig. (2-tailed)	.058	.042	.003	.051	.005	.045
	N	24	20	24	20	24	20
Spatial Span (WMS-III)	Pearson Correlation	.475*	.451*	.098	.311	.298	.395
	Sig. (2-tailed)	.019	.046	.648	.182	.158	.085
	N	24	20	24	20	24	20
Letter Number Sequence (LNS)	Pearson Correlation	.688***	.651***	.593***	.782***	.721***	.740***
	Sig. (2-tailed)	.001	.002	.002	.001	.001	.001
	N	24	20	24	20	24	20
Reasoning and Problem Solving (NAB Mazes)	Pearson Correlation	.564***	.628***	.276	.440	.463*	.566***
	Sig. (2-tailed)	.004	.003	.191	.052	.023	.009
	N	24	20	24	20	24	20
Visual Learning (BVMT-R)	Pearson Correlation	.598***	.585***	.449*	.418	.586***	.511*
	Sig. (2-tailed)	.002	.007	.028	.066	.003	.021
	N	24	20	24	20	24	20

NB “Reduced TRS” set excluded the 4 VIQ>PIQ participants.

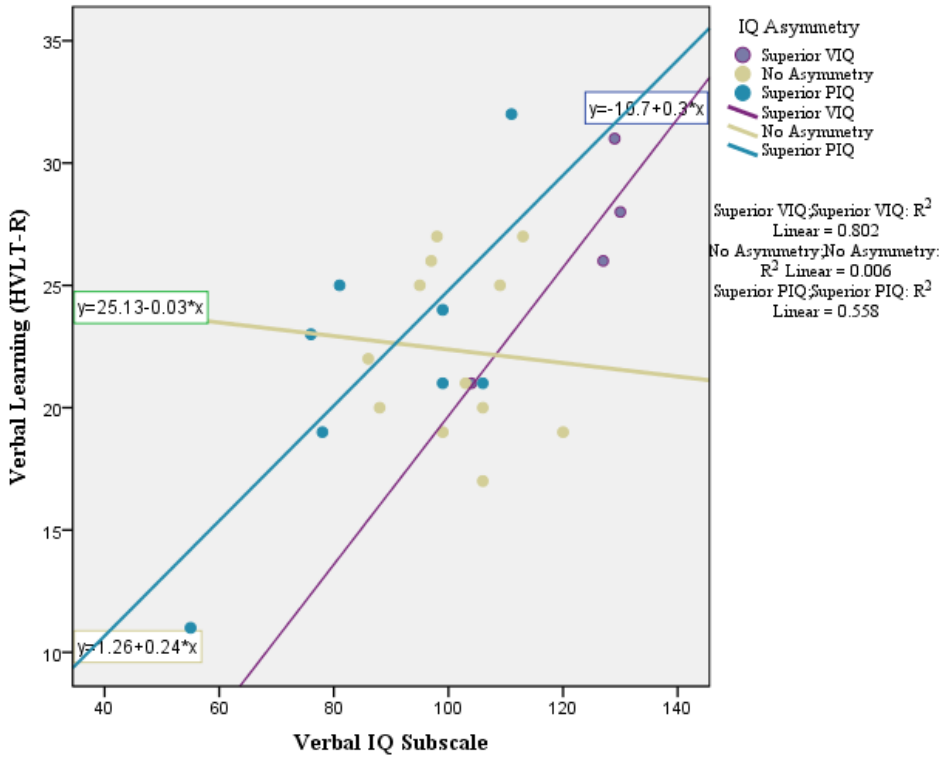
Colour coded to indicate general pattern: green indicates possible “trend” significance ($p < .09$), pale yellow * (significant at $p = .05$);
deep yellow *** (significant at $p = .001$)

Continued next page ....

Table Appx. 5. 4 continued: Associations between MCCB performance and Estimated IQ in the Full and Reduced TRS Sets

		PIQ	PIQ (reduced set)	VIQ	VIQ (reduced set)	FIQ	FIQ (reduced set)
Category Fluency (animal names)	Pearson Correlation	.532**	.609**	.246	.474*	.395	.529*
	Sig. (2-tailed)	.007	.004	.247	.035	.056	.016
	N	24	20	24	20	24	20
Social Cognition (MSCEIT ME)	Pearson Correlation	.148	.277	.408*	.445*	.340	.404
	Sig. (2-tailed)	.489	.238	.048	.050	.104	.077
	N	24	20	24	20	24	20
Sustained Attention/ Vigilance (CPT-IP)	Pearson Correlation	.315	.586**	.546**	.497*	.543**	.578**
	Sig. (2-tailed)	.143	.008	.007	.031	.007	.009
	N	23	19	23	19	23	19
Speed of Processing Composite (TMT+BACS+Fluency)	Pearson Correlation	.243	.240	.206	.177	.242	.207
	Sig. (2-tailed)	.252	.308	.333	.454	.254	.381
	N	24	20	24	20	24	20
Working Memory Composite (LNS+WMS-III)	Pearson Correlation	.699**	.649**	.409*	.634**	.608**	.664**
	Sig. (2-tailed)	.000	.002	.047	.003	.002	.001
	N	24	20	24	20	24	20

Figure Appx. 5. 6 Positive Correlation between Verbal learning (HVLT-R) and the Verbal IQ Subscale with participants grouped according to IQ asymmetry



n=4 (16%) superior scores on the verbal IQ subscale; n=9 (36%) superior scores on the performance IQ subscales; n=12 (48%) no asymmetry between the subscales

Note: Outlier (bottom left) may be distorting line of best fit for PIQ>VIQ grouping.

The prediction that VIQ might correlate with verbal learning (HVLT-R), was also supported by a strong positive correlation: r = .578, n=24, p = .003. Notwithstanding this, the correlation may have been undermined by the lack of correlation in the "no asymmetry grouping" with no asymmetry between IQ subscales, (n=12) where 5 individuals had good VIQ scores but poor verbal learning.

APPENDIX 6:

Correlational Analyses of the Haemodynamic Response at different levels of Cognitive Load with Attention (SDs in the 0-Back condition) in the TRS Group

- *positive correlations*

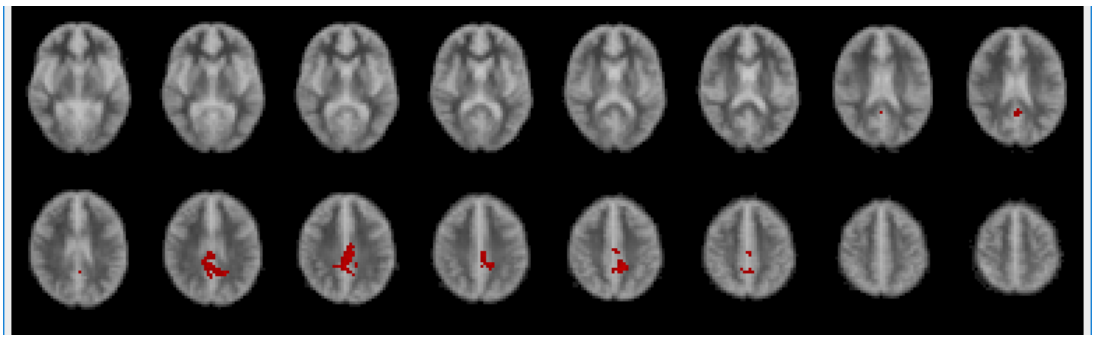
Table Appx. 6. 1 Brain areas showing significant positive correlation between SDs in the 0-Back condition and the haemodynamic response at different levels of cognitive load in the TRS group

Anatomical Location	Brodmann Area	Hemis-phere	Cluster size (mm^3)	p-Value	Talairach co-ordinates* x	y	z
1-BACK							
Cingulate Gyrus	BA 31	L	133	0.00348	-11	-37	40
2-BACK							
Non-significant.							
3-BACK							
Non-significant.							

Voxel-wise p-value = <0.05, cluster-wise p= 0.01.
Note: Age and reaction times in the baseline condition of the N-Back task were covariates.

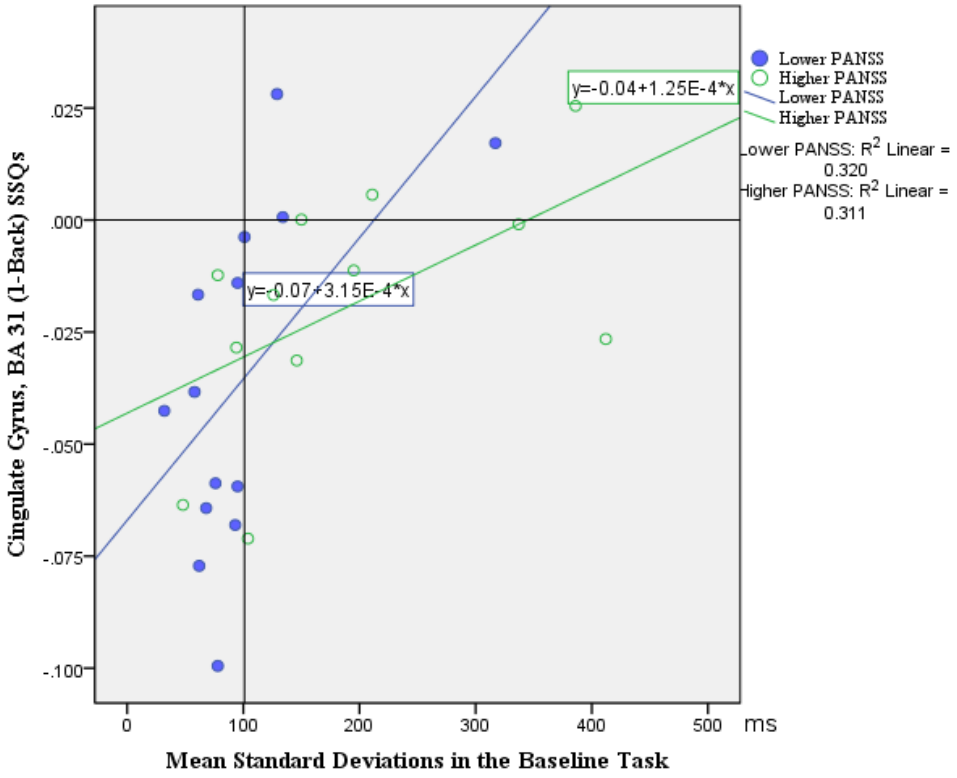
Figure Appx. 6. 1 Statistical Map of a significant positive correlation between SDs in the 0-Back condition and the haemodynamic response in the left Cingulate Gyrus (BA 31) during the 1-Back condition in the TRS Group

1-BACK



Positive correlation between SDs in the 0-Back condition the Cingulate Gyrus (BA 31).

Figure Appx. 6. 2 Positive correlation between and SDs in the 0-Back condition and the haemodynamic response in the left Cingulate Gyrus (BA 31) during the 1-Back condition in the TRS group



Note: Vertical Line indicates the median value of baseline standard deviations at 101 ms. Lines of best fit shown for lower and higher PANSS subgroups, n=14, n=12.

- *negative correlations*

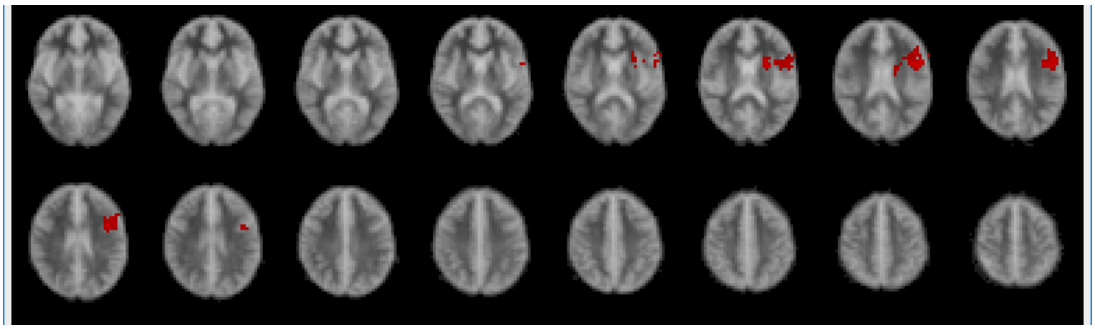
Table Appx 6. 2 Brain areas showing significant negative correlations between SDs in the 0-Back condition and the haemodynamic response at different levels of cognitive load in the TRS group

Anatomical Location	Brodmann Area	Hemis-phere	Cluster size (mm^3)	p-Value	Talairach co-ordinates* x	y	z
1-BACK							
Claustrum	-	L	167	0.00133	-25	4	17
2-BACK							
Precuneus	BA 31	R	143	0.00240	25	-67	20
3-BACK							
Medial Frontal Gyrus	BA 10	R	117	0.00266	14	48	10
Precuneus	BA 7	R	111	0.00324	25	-67	33

Voxel-wise p-value = <0.05, cluster-wise p= 0.01.
Note: Age and reaction times in the baseline condition of the N-Back task were covariates.

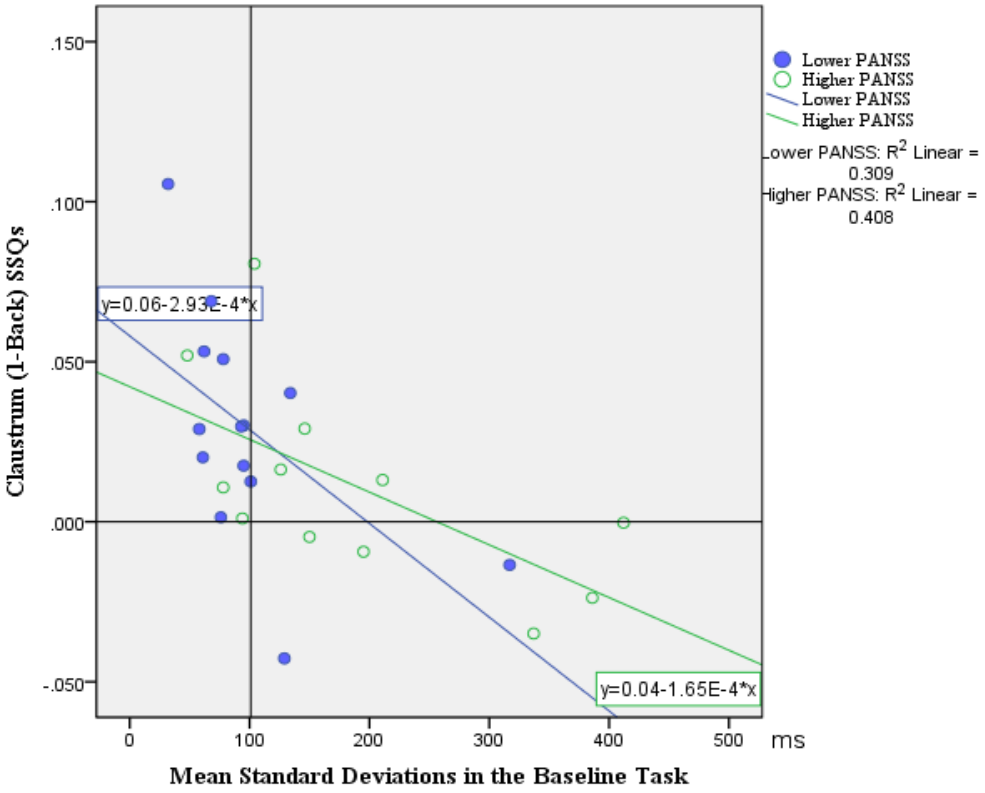
Figure Appx. 6. 3 Statistical Map showing a significant negative correlation between SDs in the 0-Back condition and the haemodynamic response in the left Claustrum during the 1-Back condition in the TRS Group

1-BACK



Negative correlation between SDs in the 0-Back condition left Claustrum, anteriorly.

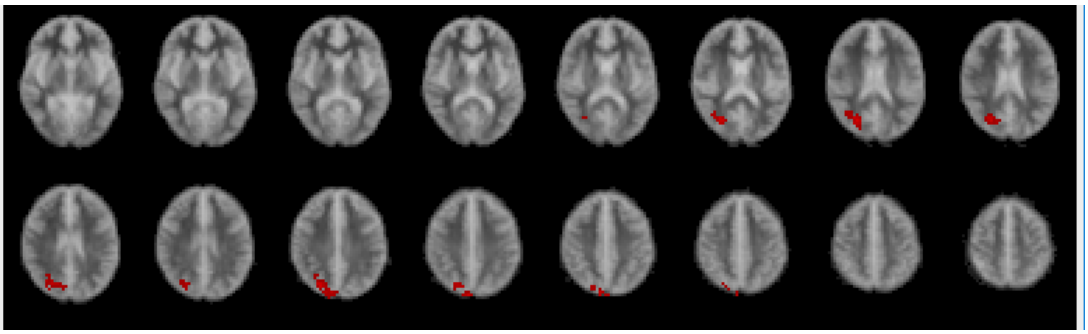
Figure Appx. 6. 4 Negative correlation between SDs in the 0-Back condition and the haemodynamic response in the left Claustrum during the 1-Back condition in the TRS group



Note: Vertical Line indicates the median value of baseline standard deviations at 101 ms. Lines of best fit shown for lower and higher PANSS subgroups, n=14, n=12.

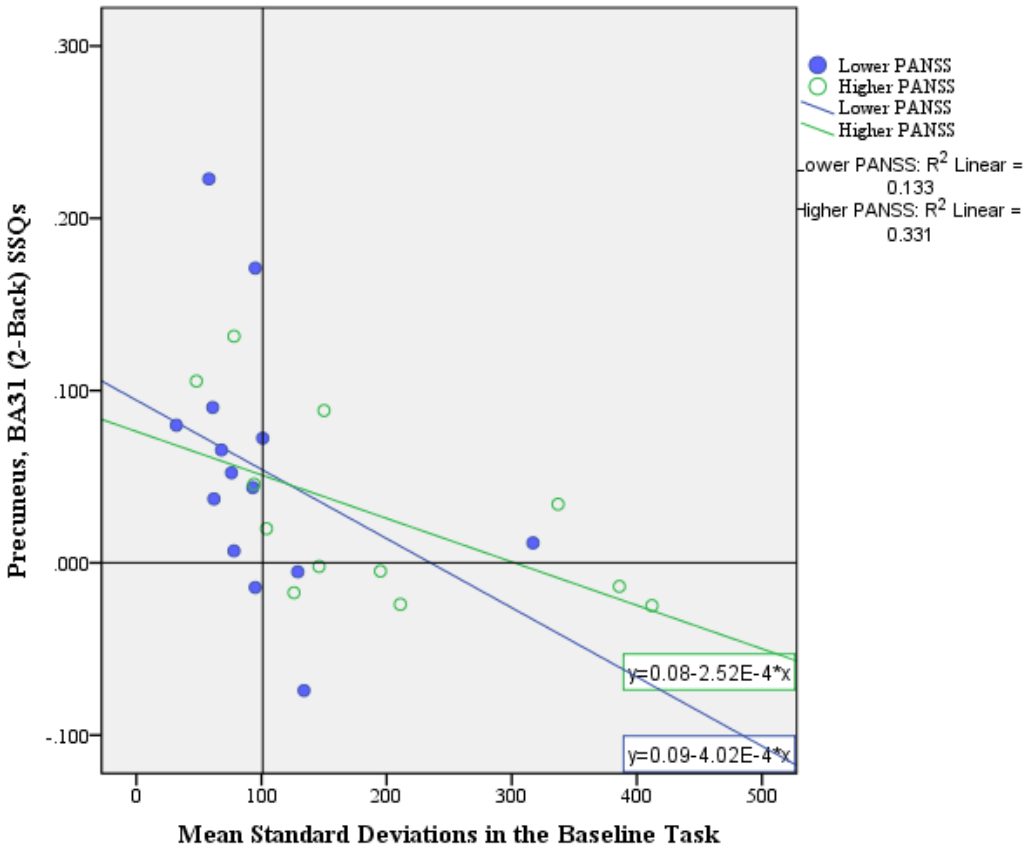
Figure Appx. 6. 5 Statistical Map showing a significant negative correlation between SDs in the 0-Back condition and the haemodynamic response in the right Precuneus (BA 31) during the 2-Back in the TRS Group

2-BACK



Negative correlation between SDs in the 0-Back condition and the right Precuneus (BA 31)

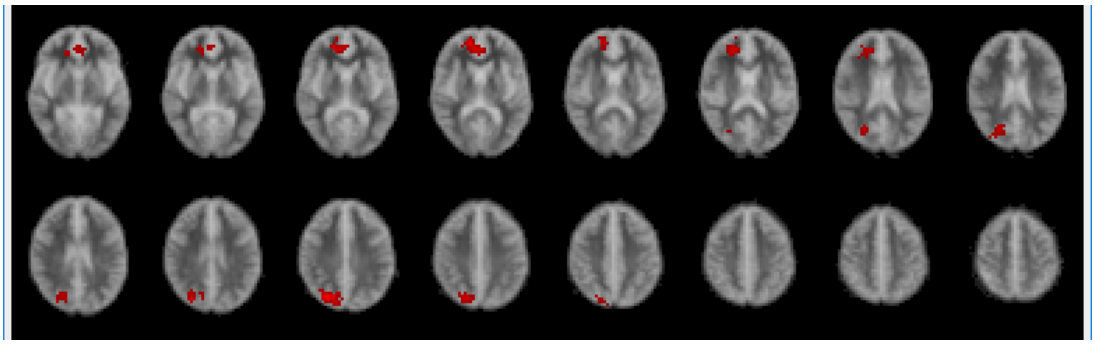
Figure Appx. 6. 6 Negative correlation between SDs in the 0-Back condition and the haemodynamic response in the right Precuneus (BA 31) during the 2-Back condition in the TRS group



Note: Vertical Line indicates the median value of baseline standard deviations at 101 ms.
Lines of best fit shown for lower and higher PANSS subgroups, n=14, n=12.

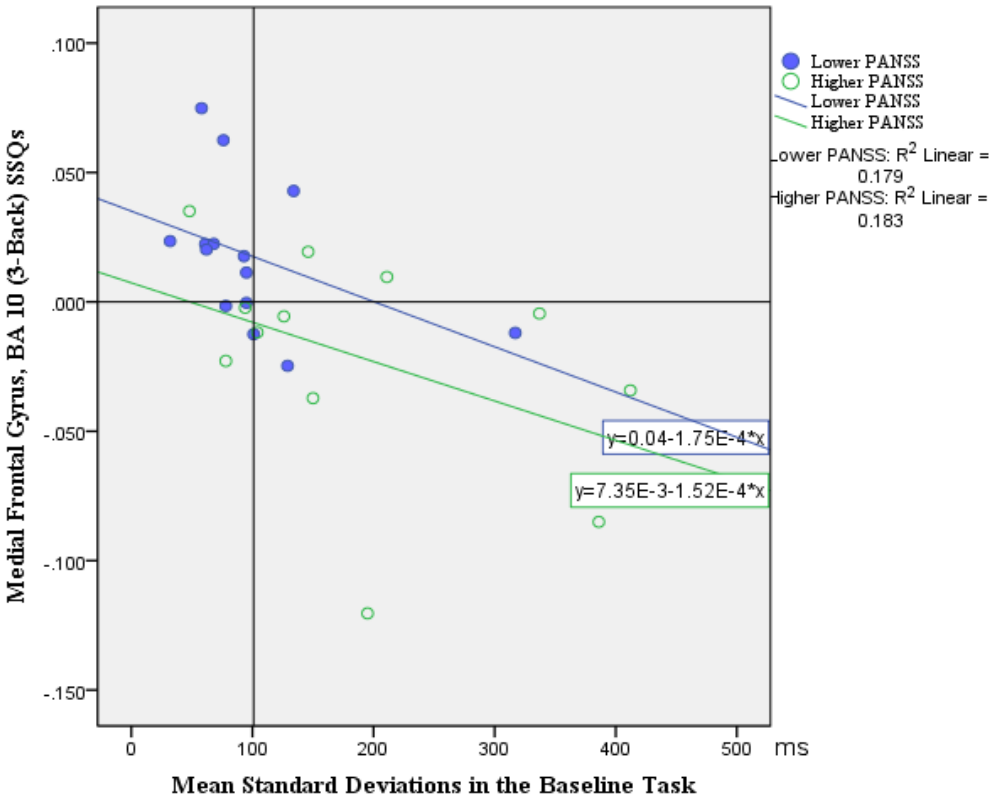
Figure Appx. 6. 7 Statistical Map showing significant negative correlations between SDs in the 0-Back condition and the haemodynamic response in the right Medial Frontal Gyrus (BA 10) and right Precuneus (BA 7) during the 3-Back condition in the TRS group

3-BACK



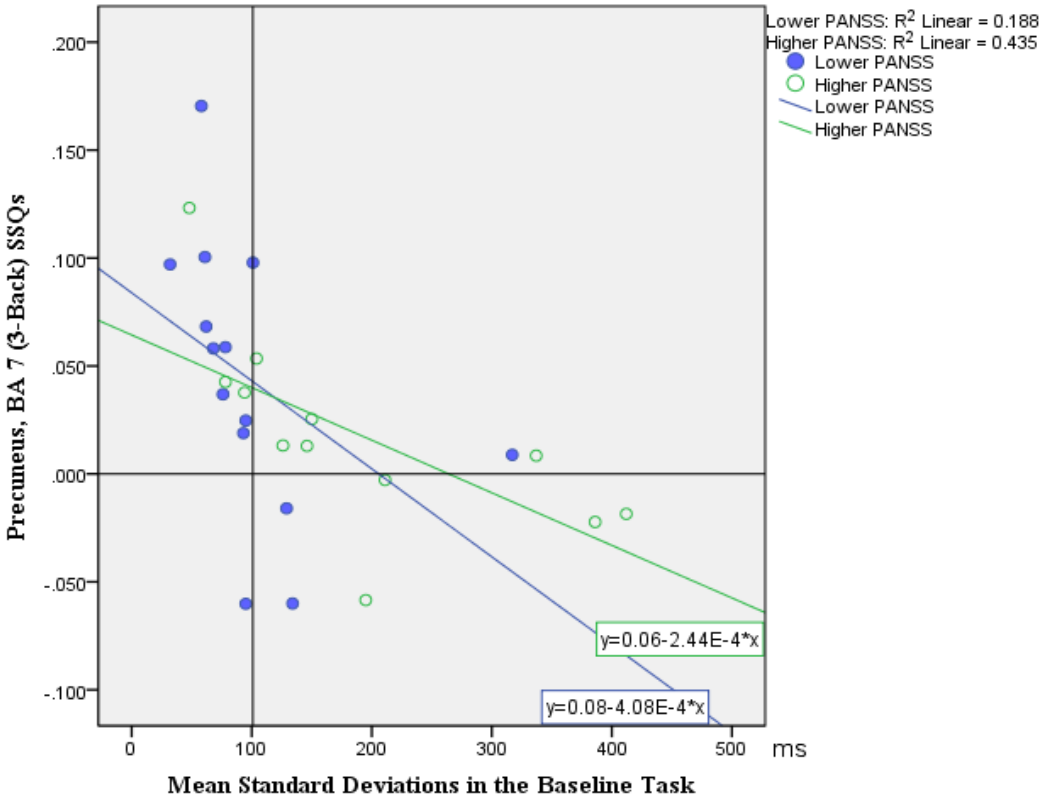
Negative correlation between SDs in the 0-Back condition and the right Medial Frontal Gyrus (BA 10) and right Precuneus (BA 7).

Figure Appx. 6. 8 Negative correlation between the haemodynamic response in the right Medial Frontal Gyrus (BA 10) in the 3-Back condition and SDs in the 0-Back in the TRS group (3-Back).



Note: Vertical Line indicates the median value of baseline standard deviations at 101 ms.
Lines of best fit shown for lower and higher PANSS subgroups, n = 14, n = 12.

Figure Appx. 6. 9 Negative correlation between SDs in the 0-Back condition and the haemodynamic response in the right Precuneus (BA 7) during the 3-Back condition in the TRS group



Notes: Vertical line above indicates the median value of the baseline standard deviations at 101ms. Lines of best fit shown for lower and higher PANSS subgroups, n = 14, n =12.

Correlational Analyses of the Haemodynamic Response at different levels of Cognitive Load with Attention (SDs in the 0-Back condition) in the Control Group

- *positive correlations*

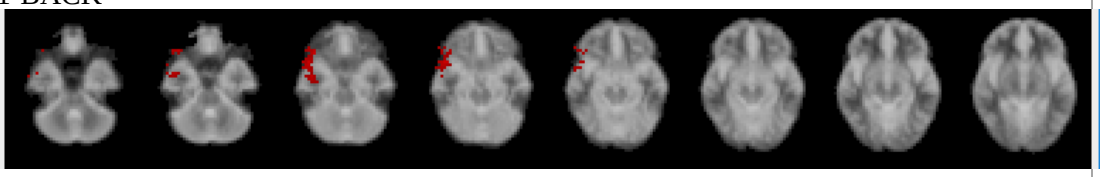
Table Appx. 6. 3 Brain areas showing significant positive correlations between SDs in the 0-Back condition and the haemodynamic response and at different levels of cognitive load in the Control group

Anatomical Location	Brodmann Area	Hemis-phere	Cluster size (mm^3)	p-Value	Talairach co-ordinates* x	y	z
1-BACK							
Superior Temporal Gyrus	BA 38	R	109	0.00269	61	11	-20
2-BACK							
Non-significant							
3-BACK							
Non-significant							

Voxel-wise p-value = <0.05, cluster-wise p= 0.01.
Note: Age and reaction times in the baseline condition of the N-Back task were covariates.

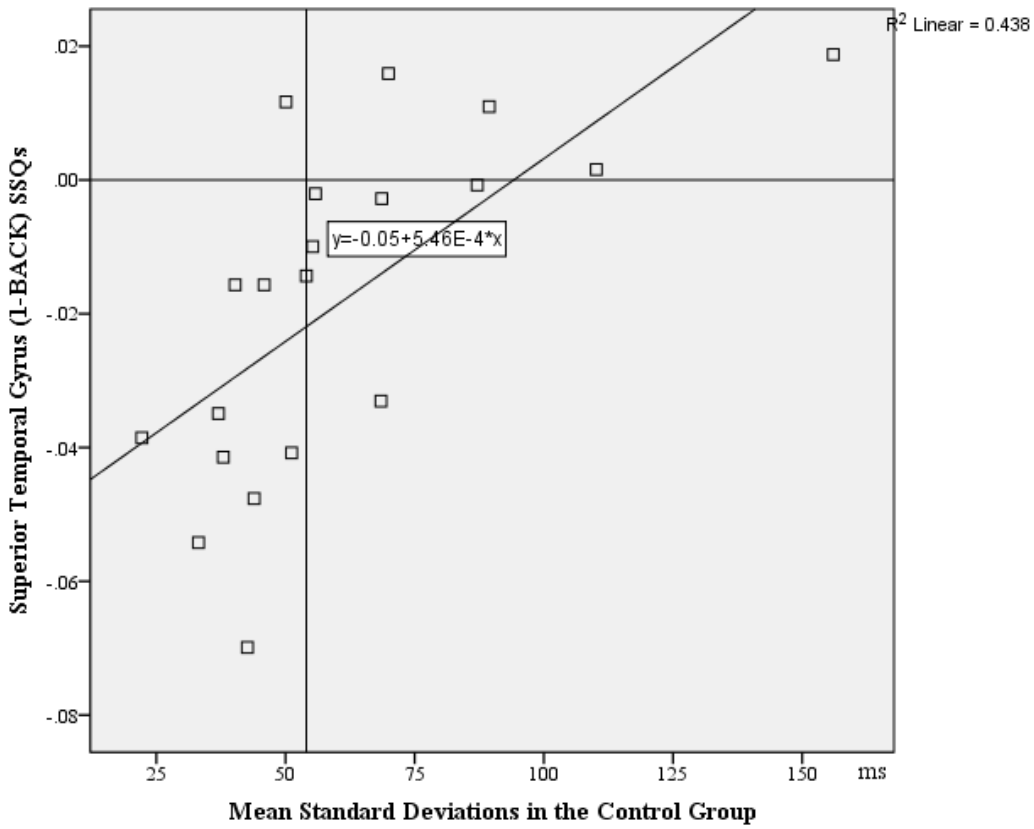
Figure Appx. 6. 10 Statistical Map of a positive correlation between SDs in the 0-Back condition and the haemodynamic response in the right Superior Temporal Gyrus (BA 38) in the Control Group

1-BACK



Positive correlation between SDs in the 0-Back condition and the right Superior Temporal Gyrus (BA 38).

Figure Appx. 6. 11 Positive correlation between SDs in the 0-Back condition and the haemodynamic response in the right Superior Temporal Gyrus (BA 38) during the 1-Back condition in the Control group



Note: Vertical line indicates median of SDs in the baseline condition of the N-Back task in the control group at 54.03ms. N = 21 (except graph based on n = 20 after outlier removed).

- *negative correlations*

Table Appx. 6. 4 Brain areas showing significant negative correlation between SDs in the 0-Back condition and the haemodynamic response at different levels of cognitive load in the Control group

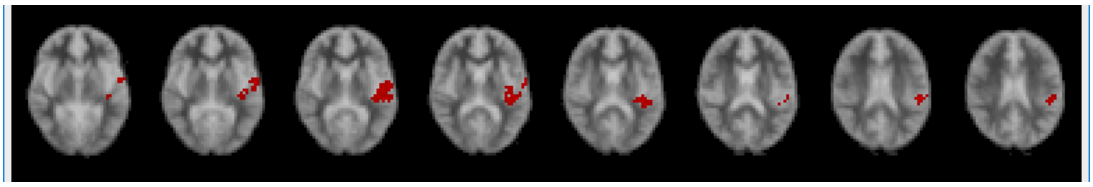
Anatomical Location	Brodmann Area	Hemis-phere	Cluster size (mm^3)	p-Value	Talairach co-ordinates* x	y	z
1-BACK							
Transverse Temporal Gyrus	BA 41	L	151	0.00193	-47	-26	10
2-BACK							
Precuneus	BA 7	R	97	0.00319	25	-59	30
3-BACK							
Non-significant.							

Voxel-wise p-value = <0.05, cluster-wise p= 0.01.

Note: Age and reaction times in the baseline condition of the N-Back task were covariates.

Figure Appx. 6. 12 Statistical Map showing significant negative correlation between SDs in the 0-Back condition and the haemodynamic response in the left Transverse Temporal Gyrus (BA 41) during the 1-Back condition in the Control Group

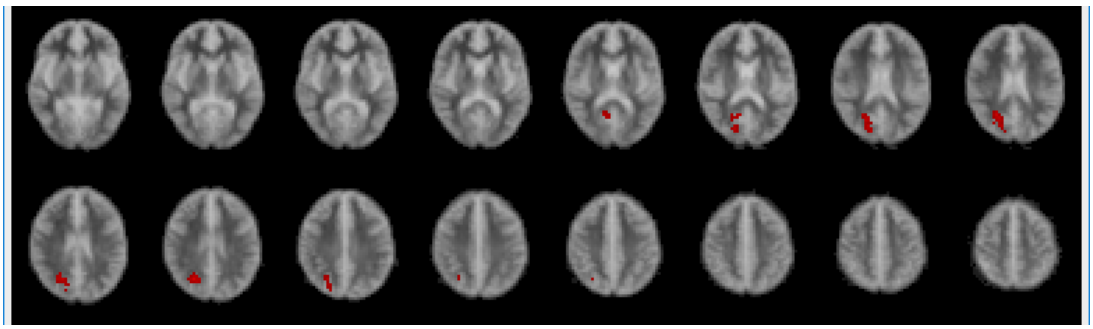
1-BACK



Negative correlation between SDs in the 0-Back condition and the left Transverse Temporal Gyrus (BA 41).

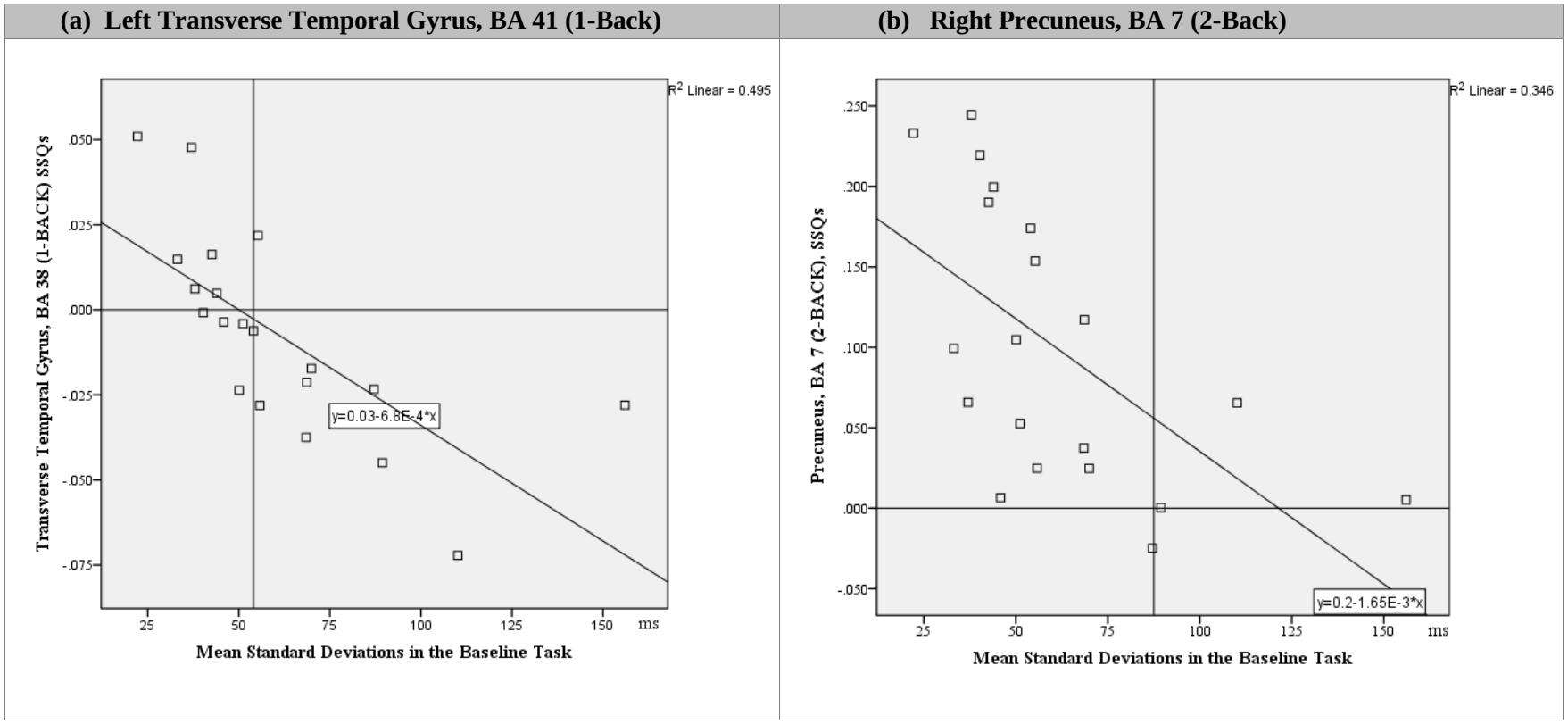
Figure Appx. 6. 13 Statistical Map showing a significant negative correlation between SDs in the 0-Back condition and the haemodynamic response in the right Precuneus (BA7) during the 2-Back condition in the Control group

2-BACK



Negative correlation between SDs in the 0-Back condition and the haemodynamic response in the right Precuneus (BA 7).

Figure Appx. 6. 14 Negative correlations between SDs in the 0-Back condition and the haemodynamic response in the left Transverse Temporal Gyrus during the 1-Back condition and the right Precuneus during the 2-Back in the Control Group



Notes: Vertical line = median of SDs in the baseline condition of the N-Back task at 54.03ms, n=21.
The graphs are based on n=20 after an outlier was removed for depiction purposes.

Correlational Analyses of the Haemodynamic Response at different levels of Cognitive Load with Estimated Full-Scale IQ and Subscales in the TRS Group

- *positive correlations*

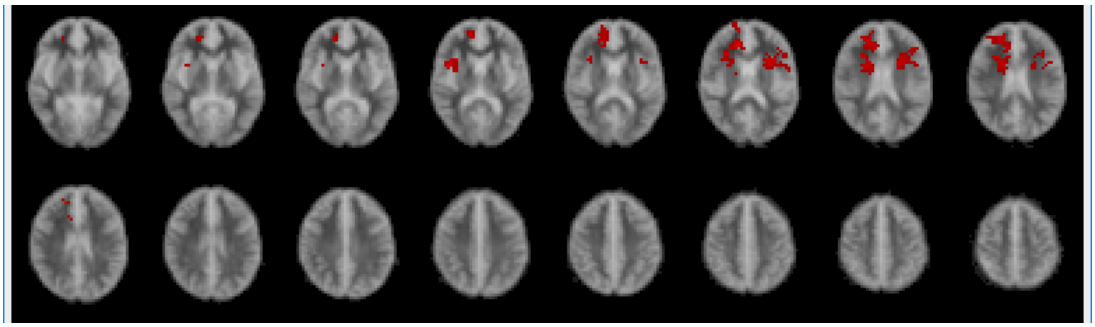
Table Appx. 6. 5 Brain areas showing significant positive correlation between FIQ scores and the haemodynamic response at different levels of cognitive load in the TRS group

Anatomical Location	Brodmann Area	Hemis-phere	Cluster size (mm^3)	p-Value	Talairach co-ordinates* x	y	z
1-BACK							
Insula	BA 13	L	88	0.00377	-33	15	17
Insula	BA 13	R	210	0.00068	43	7	10
2-BACK							
Non-significant.							
3-BACK							
Non-significant.							
Correlation with scores on the Verbal IQ Subscale in the 1-Back Condition:							
Inferior Frontal Gyrus	BA 13	L	196	0.00102	-43	26	10

Voxel-wise p-value = <0.05, cluster-wise p= 0.01.
Note: Age and mean reaction times in the baseline N-Back condition were covariates.

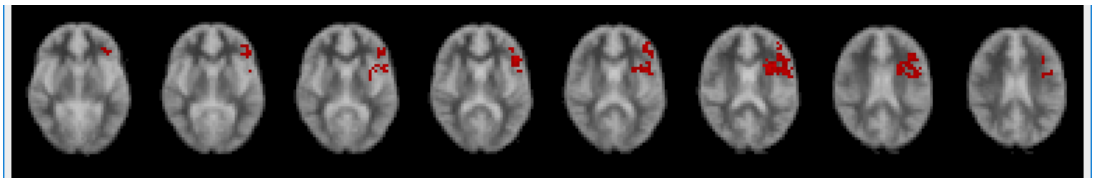
Figure Appx. 6. 15 Statistical map showing significant positive correlation between FIQ scores and the haemodynamic response in the Insula bilaterally during the 1-Back condition in TRS Group, also between VIQ and the left Inferior Frontal Gyrus (BA 13)

1-BACK



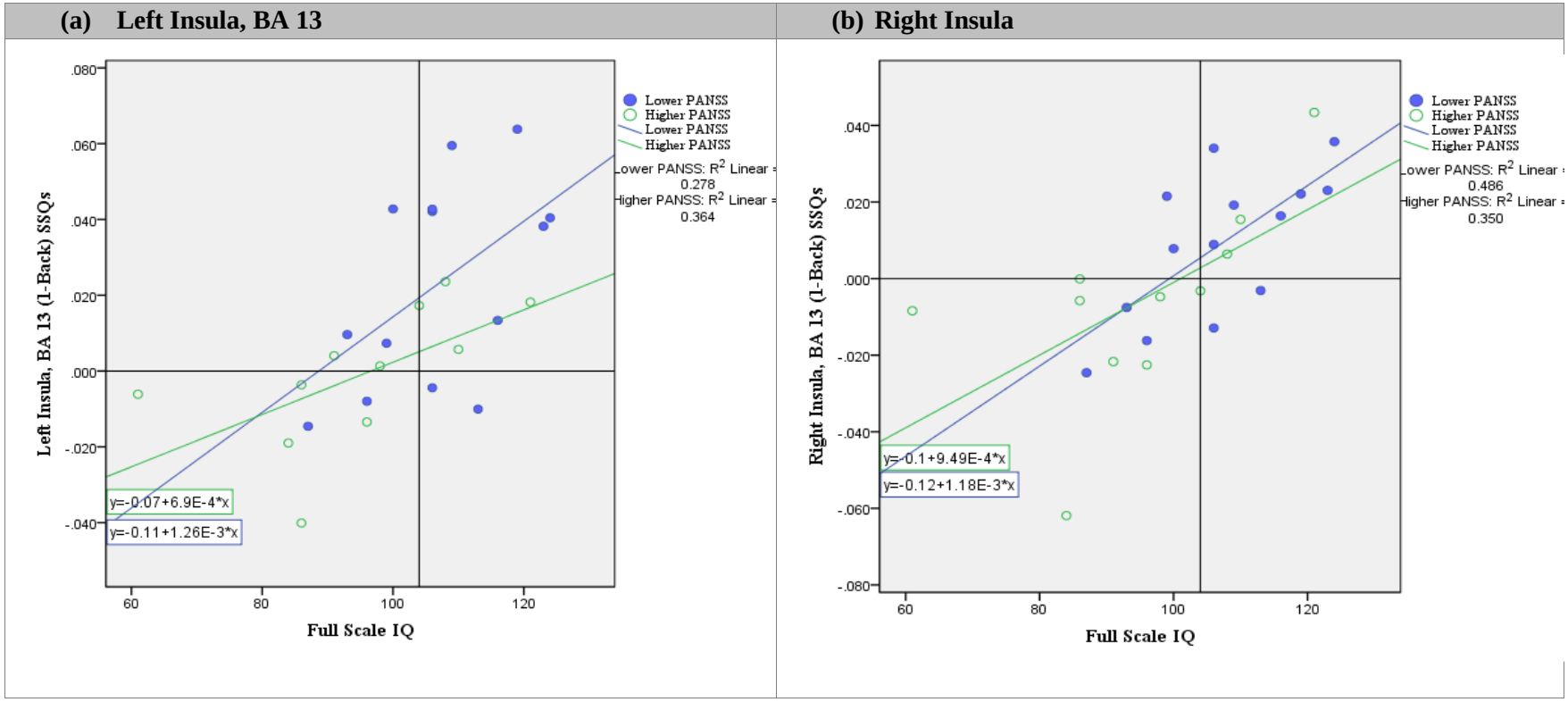
Positive correlation with Full-scale IQ scores in the insula (BA 13) bilaterally.

1-BACK



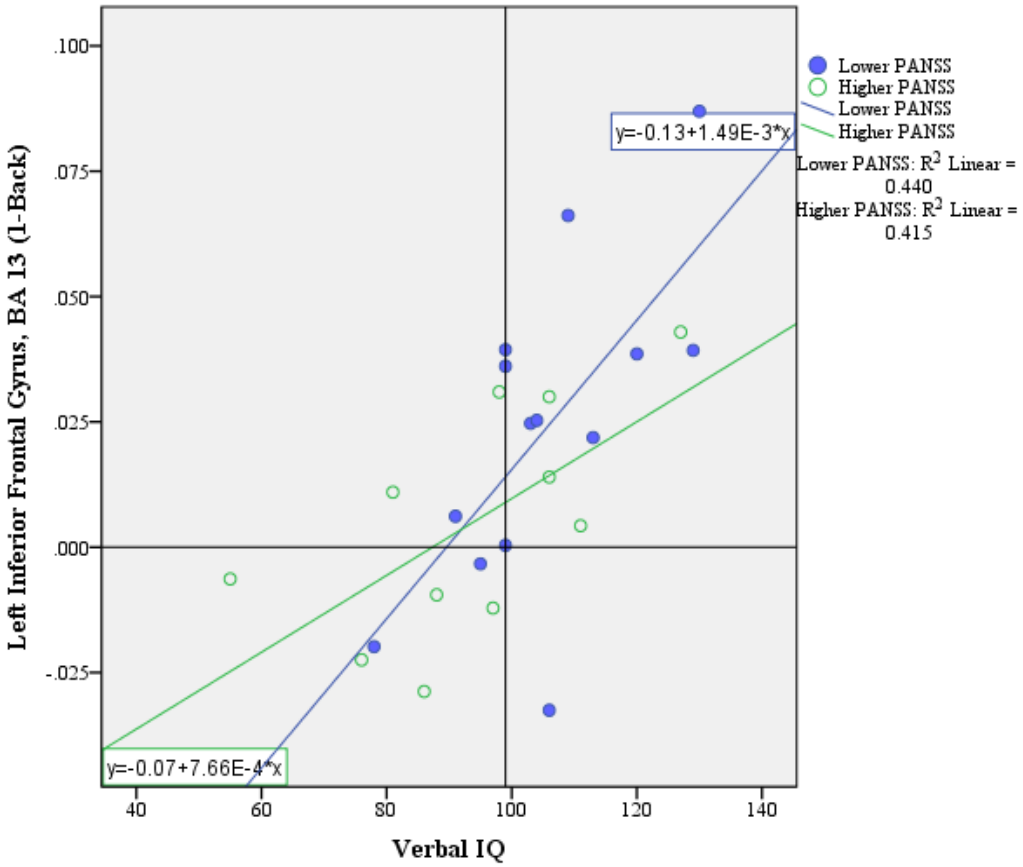
A positive correlation was also observed between Verbal IQ subscale scores and the haemodynamic response in the left inferior frontal gyrus (BA 13).

Figure Appx. 6. 16 Positive Correlations between FIQ scores and the haemodynamic response in the Insula (BA 13) bilaterally during the 1-Back Condition



Notes: Vertical line = median of estimated Full-scale IQ at 104 in the TRS group, n = 25. Lines of best fit show lower and higher PANSS subgroups, n=13, n=12.

Figure Appx. 6. 17 Positive Correlation between Verbal IQ subscale scores and the haemodynamic response and the left Inferior Frontal Gyrus (BA 13) in the 1-Back



- *negative correlations*

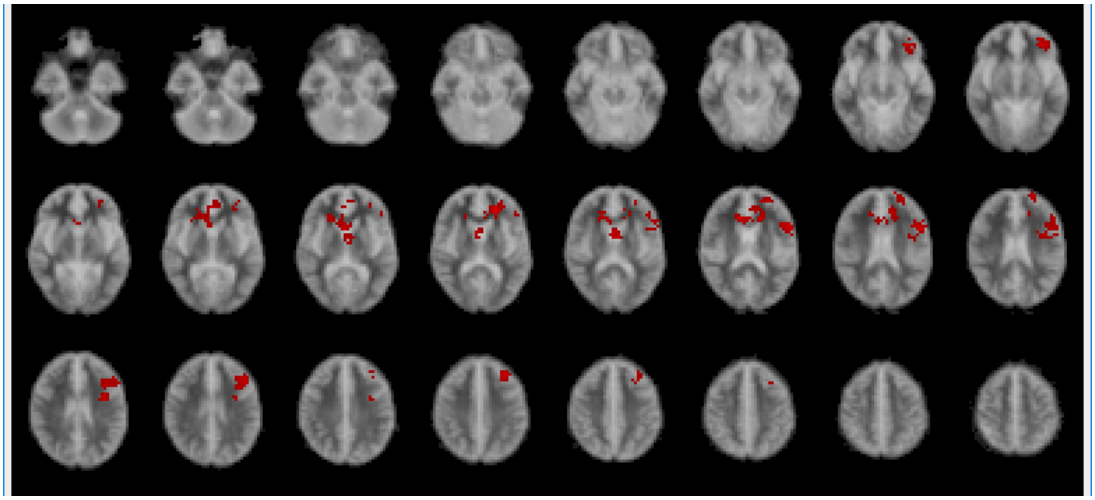
Table Appx. 6. 6 Brain areas showing significant negative correlations between FIQ scores and the haemodynamic response at different levels of cognitive load in the TRS group

Anatomical Location	Brodmann Area	Hemis-phere	Cluster size (mm^3)	p-Value	Talairach co-ordinates* x	y	z
1-BACK							
Non-significant							
2-BACK							
Non-significant							
3-BACK							
Anterior Cingulate	BA 32	L	129	0.00294	-18	37	10
Anterior Cingulate	BA 32	R	136	0.00348	8	29	22
Inferior Frontal Gyrus	BA 44	L	171	0.00163	-54	11	17

Voxel-wise p-value = <0.05, cluster-wise p= 0.01.
Note: Age and reaction times in the baseline condition of the N-Back task were covariates.

Figure Appx. 6. 18 Statistical Map showing significant negative correlations between FIQ and the haemodynamic response in the Anterior Cingulate (BA 32) bilaterally and in the left Inferior Frontal Gyrus (BA44) during the 3-Back condition

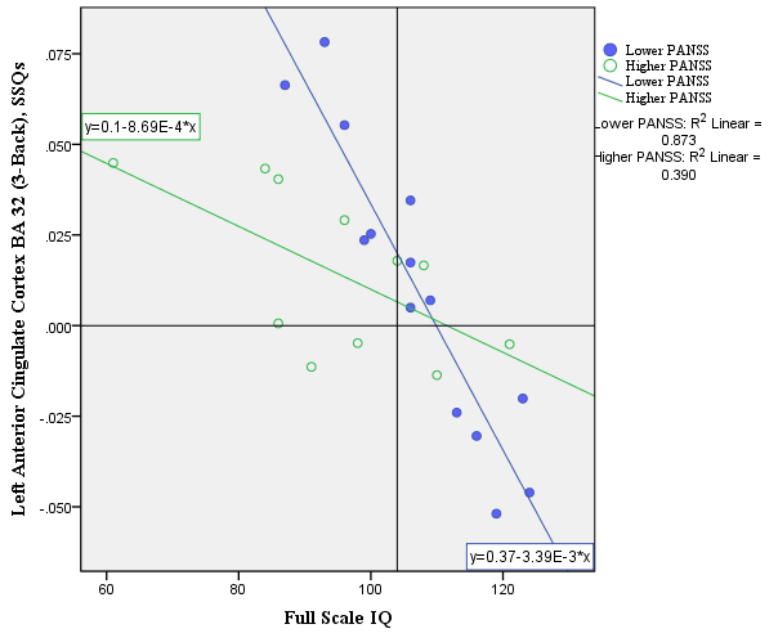
3-BACK

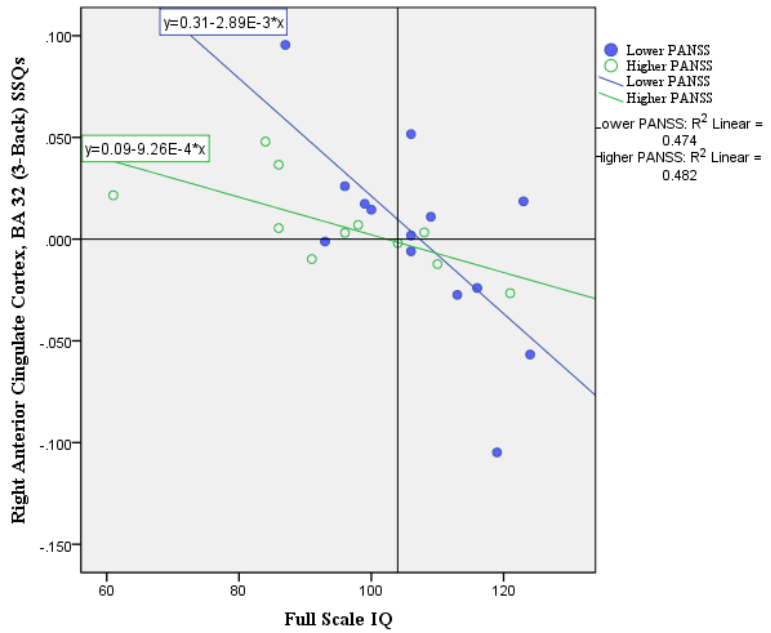


Negative correlations between FIQ scores in the TRS Group and the haemodynamic response in the Anterior Cingulate Gyrus, BA 32 bilaterally and the left Inferior Frontal Gyrus, BA 44.

Figure Appx. 6. 19 Negative correlations between FIQ scores and the haemodynamic response in the Anterior Cingulate (BA 32) bilaterally and the 3-Back Condition

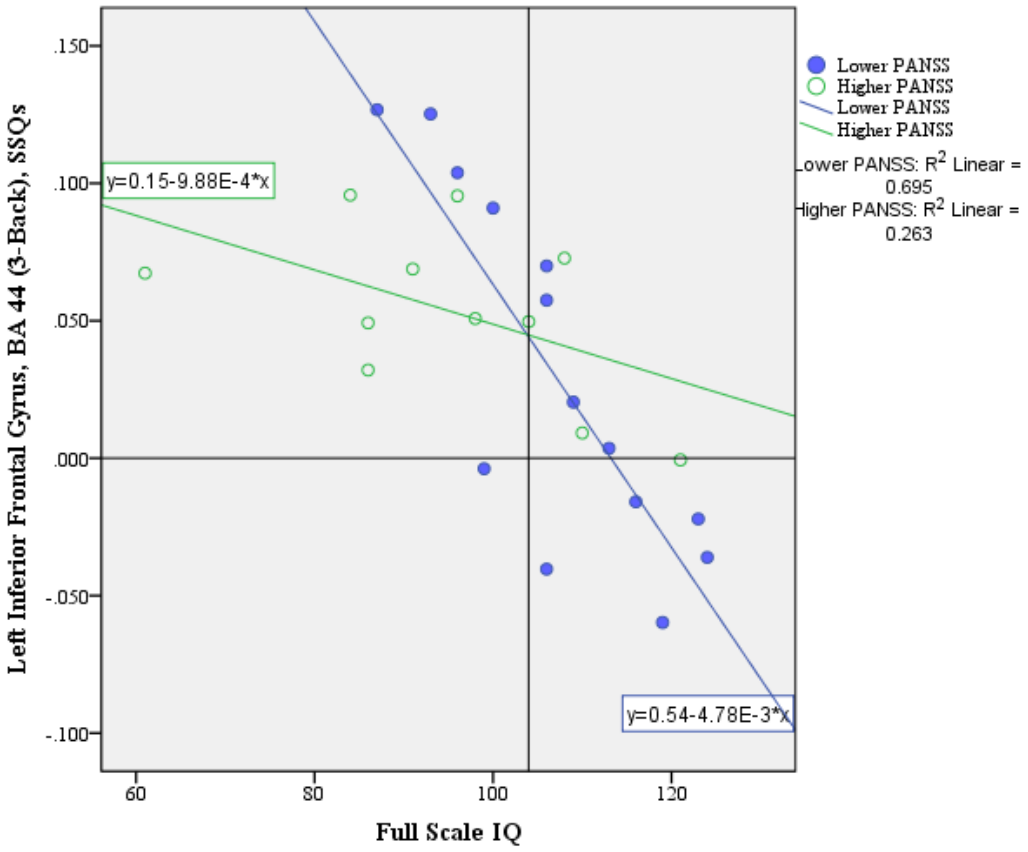
(a) Left Anterior Cingulate, BA 32	(b) Right Anterior Cingulate, BA 32





Notes: Vertical line = median of estimated Full-scale IQ at 104 in the TRS group, n = 25. Lines of best fit show lower and higher PANSS subgroups, n=13, n=12.

Figure Appx. 6. 20 Negative correlation between FIQ scores and the haemodynamic response in the Inferior Frontal Gyrus (BA 44) during the 3-Back Condition in the TRS group



Notes: Vertical line = median of estimated Full-scale IQ at 104 in the TRS group, n=25. Lines of best fit shown for lower and higher PANSS subgroups, n=13, n=12

APPENDIX 7:

Sample Participant Information Sheet and Consent Forms

PARTICIPANT INFORMATION SHEET

PART 1:

•**Project Title: Neuroanatomy of working memory and drug-response in schizophrenia**

•**Invitation:**

We are inviting you to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and talk to others about the study if you wish. Thank you for considering taking part.

- Part 1 outlines the purpose of this study and your role in it if you take part.
- Part 2 gives you more detailed information about the conduct of the study.

Please ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

•**Purpose of the Study:**

The purpose of this research is to investigate the way the medication you are taking works. This study will look specifically at which brain areas are involved in certain memory tasks. It will involve a structural magnetic resonance imaging (sMRI) scan and two functional MRI brain scans (fMRI).

•**Why have I been chosen?:**

Because you are attending an Outpatient Clinic.

•**Do I have to take part?:'**

No. It is up to you to decide whether or not to take part. If you do, you will be given this information sheet to keep and be asked to sign a consent form. You will still be free to withdraw from the study at any time and without giving a reason.

•**What will happen if I take part?**

You will be invited to spend about half a day at the Institute of Psychiatry where you will be met in the main reception and taken to a more private area where you will be given a brief

overview of the schedule of activities and asked to sign a consent form (remembering, of course, that you can withdraw at any time without giving a reason). You will also be asked some general background questions, for example, about your age and current occupation.

During your time at the Institute you will be asked to complete a series of short psychological tasks. Some of these tasks with be presented to you by a researcher who will ask you for instance to copy geometric patterns using small building blocks, to find similarities between words, and to give the meaning of individual words as if you were a dictionary, for example, "what is a crocodile?". Some other tasks will involve pressing buttons or clicking on a computer screen with a cursor, for example, to indicate the location of a dot that was displayed previously.

Before accompanying you to the MRI scanner the researcher will give you the opportunity to practice on a couple of tasks which we will then ask you to perform while having a functional brain scan (which will take about one hour). These tasks are computer-based and involve memory and attention. For example, you will be asked to indicate if you recognize a letter on a computer screen as having occurred shortly beforehand; also to tap out patterns using three fingers. You will have plenty of practice at these tasks before you go into the scanner. The scanner consists of a large magnet which does not emit radiation and you will not be asked to take any drugs. During the scan we will make an image of the structure of your brain, as well as collecting lots of images of your brain as you perform the tasks described in this paragraph. A structural MRI scan lasting 7 minutes will be also collected, during which we'll ask you to rest and even sleep if you feel like.

Lastly, you'll be asked to give a blood sample in order to collect genetic information which we will investigate in relation to your brain scan. This will help us to investigate whether certain genetic variations are associated with the way the brain works and responds to the antipsychotic medication you are taking.

•**Expenses and payments:**

Each participant will receive £30 for taking part in the study. We'll also cover your travel expenses if necessary.

•**What do I have to do?:**

You will have the opportunity to ask the radiographer any questions you may have before you enter the scanner. When you are in the scanner you will be asked to keep as still as possible. Some people find the scanner noisy or uncomfortable as you go into a small space.

As the scanner is a magnet it may attract certain metallic objects. Therefore you must not have a scan if you have received metal injuries to the eye, had metallic objects (including clips) inserted in your body during an operation, or you have received a shotgun injury, or have a heart pacemaker. During your scan we can talk to you and you can talk to us and you can be brought out of the scanner if you wish. While you are in the scanner the psychologist conducting the study will be on the other side of the screen making sure that everything runs smoothly. You can ask her any question that you may have at any time.

•**What is the device or procedure that is being tested?:**

The scanner consists of a large magnet, it does not emit radiation and you will not be asked to take any drugs. Use of that device will allow us to monitor the activity in your brain during performance of the mental operations (tasks) mentioned above.

•**What are the alternatives for diagnosis and treatment?:**

We do not expect to find anything of concern in your scan. However, if we do we will contact your GP with your permission.

•**What are the side effects of any treatment received when taking part?:**

Magnetic Resonance imaging (MRI) is an absolutely safe method which does not contain any radiation or cause any side effect.

•**What are the other possible disadvantages and risks of taking part?:**

You might experience some discomfort in the scanner as you will have to remain still in a small enclosed space and periodically it will be very noisy. You can leave the scanner at any time if you cannot tolerate it.

•**What are the possible benefits of taking part?:**

By taking part in the study you may help in the future other client users with problems similar to those you are a experiencing. We are hoping this investigation will help us to predict which individuals with schizophrenia may not benefit from certain drugs and enable them to access more suitable treatment.

•**What happens when the research study stops?:**

Results will be published in medical journals and all participants will be sent a summary of the findings.

•**What if there is a problem?:**

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. Contact number for complaints: Dr Chiara Nosarti, 0207 848 0133.

•**Will my taking part in the study be kept confidential?**

Yes. All the information about your participation in this study will be kept confidential (Details included in part 2).

•**Contact Details:**

For further information about the study please do not hesitate to contact Mrs Hazel Sparey on 07850 985588 or 0207 848 0516; or Tracey Collier on 0207 848 0029. If you would like to receive independent information or advice about your rights as research subject or about being involved in this particular research study you could also contact the Patients Advice and Liaison Service (PALS) at SLaM on 0800 7312864.

This completes Part 1 of the Information Sheet. If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision

PART 2:

•**What will happen if I don't want to carry on with the study?:**

As it has been already mentioned you can withdraw from the study at any time. If you do so we will use the data collected up until your withdrawal.

•**What if there is a problem?:**

If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions (Contact number is given in part 1). If you remain unhappy and wish to complain formally, you can do this through the Institute of Psychiatry. King's College London, indemnity arrangements will apply.

•**Will my taking part in the study be kept confidential?:**

Information about the participants will be held in confidence and numerical codes will be used to identify participants on computer files.

•**Will genetic tests be done?:**
A blood sample will be drawn by trained staff for genetic testing. This will enable the influence of hereditary traits in psychotic conditions to be assessed and hence potentially improve treatment.

•**Are there any other blood tests?**
Not directly, but Researchers will need access to periodic reports on plasma levels related to drug treatment regimes and screening for other substances which could have an influence on how patients respond to their drug therapy.

•**What will happen to the results of the study?:**
The results of the research will be published e.g. Peer reviewed scientific journals, internal reports, and conference presentations. You will not be identified in any report/publication.

•**Who is organising and funding the research?**

The National Institute for Health Research Biomedical Research Centre for Mental Health.

•**Who has reviewed this study?:**

This study was given a favourable ethical opinion by Wandsworth Research Ethics Committee.

Each participant will be given a copy of the information sheet and a signed consent form to keep.

I would like to thank you for considering taking part and taking time to read this sheet.

Participant Consent Form

Participant Consent Form

Title of project:

Neuroanatomy of working memory and drug response in schizophrenia

The participant should complete the whole of this sheet him or herself.
(please tick each statement if it applies to you)

I have read the Information Sheet ☐

I have been given the opportunity to ask questions and discuss this study. ☐

I have received satisfactory answers to all my questions. ☐

I have received enough information about the study. ☐

I give permission for the researchers to view my medical records, and I understand that the information will be kept confidential. ☐

I give permission for my doctor to be informed if any of the tests done as part of the research are important for my health ☐

I understand that I will not benefit financially if the research leads to the development of commercial products. ☐

I agree to give a sample of blood for research and understand how the sample will be collected. ☐

I understand that the research using the blood sample may include research aimed at understanding drug response in schizophrenia, but that the results are unlikely to have any implications for me personally. ☐

The study has been explained to me by:
Prof/Dr/Mr/Mrs/Ms_____

I understand that I am free to withdraw from the study at any time, without having to give a reason for withdrawing and without affecting my future medical care. ☐

I agree to take part in this study. ☐

Signed.....Date.....
(NAME IN BLOCK CAPITALS).....

Investigator's signature.....Date: .....
(NAME IN BLOCK CAPITALS).....

Social and Demographic Questionnaire

BRCMSL

DEMOGRAPHIC DETAILS

NAME:

Date Interviewed:_____ **Individual Number**: _____

Sex: Male/ Female **Height:**: **Weight:**

Date of birth: **Age in years**:

Address:

Telephone Number: _____ **Mobile Phone:** _____

Email:

Key Relative: (Name & Address)

GP: (Name & Address)

Consultant:

1 BRCMSL0_____

Migration:

Were you born in the UK?

Were your parents born in the UK?

Were your grandparents born in the UK?

Relatives:
Number of brothers: _____

Number of sisters: _____

Birth order (with same Mum): _____

Sibling order (if different): _____

Ethnicity:

Caucasian / White British

Black British

African

Afro-Caribbean,

Indian Subcontinent,

Other

Marital Status:

Single=1, Married=2, Separated=3, Divorced=4, Widowed=5, Cohabiting=6

Employment:
Are you currently working? Full-time? What kind of work do you do?
What has been your main job in the past?
Current: _____
Best Ever: _____

Occupation(s) of father / mother at birth: _____

Handedness (Annett)

Which hand to you use

to write a letter legibly		*at the top of a broom while sweeping*	
to throw a ball to hit a target		*At the top of a shovel when moving sand*	
To hold a racket in tennis,squash or badminton		*To deal playing cards*	
To hold a match whilst striking it		*To hammer a nail into wood*	
To cut with scissors		*To hold a toothbrush while cleaning your teeth*	
To guide a thread through the eye of a needle		*To unscrew the lid of a jar*	
*If you use your **RIGHT** hand for any of these actions, are there any **one handed actions** for which you use your **LEFT**? (please record them here)*			
With which eye would you look through a telescope? (Roll paper and try).			
Which foot would you use to kick a ball?			

Can you play a musical instrument?

Have you ever had any tuition?

What about singing?

Can you read music?

So would you say you have an "ear" for music?

What about rhythm?

Details if currently studying:_____

No. of Years in Education: {count 2 years ½ time as 1 year?}

Left School when?

Apprenticeships?

Armed Services?

EDUCATIONAL ATTAINMENTS
Have you done GCSEs? Yes/No
If *yes*, what grades did you get?

GCSE Subjects:	Grade:	GCSE Subjects:	Grade:
1.		5.	
2.		6.	
3.		7.	
4.		8.	

Have you done A levels? Yes/No
If *yes*, what grades did you get?

A-level subjects:	Grade:	A-level subjects:	Grade:
1.		3.	
2.		4.	

Have you done a GNVQ? Yes/No
If *yes*, in what subject(s) and at what level?

GNVQ subject:	Level:	GNVQ subject:	Level:
1.		2.	

Other Educational?

e.g. HNC

Smoking

If ever, from what age? _____

How many per day then? _____

If smoking now – how many per day? _____

Have you been a heavier smoker than at present? _____

Have you ever made a deliberate effort to cut-back or stop? _____

Stopped and when? _____

Alcohol Consumption

Do you drink alcohol regularly?

Not at all / Not regularly / Yes

At what age did you start drinking regularly? _____

Average weekly drinking pattern
(1 unit = ½ pt beer, 1 glass of wine or 1 measure of spirits)

	Mon	Tues	Wed	Thurs	Fri	Sat	Sun
Beer (pt)							
Spirits							
Wine							
Alcopop							
Total							

Have there been any time(s) when you have been drinking heavily?

During that time, how much did you drink during a typical week?

For how long did you drink that heavily?

Did you ever go on a binge/ bender? How long for? How often? (Binge defined as continuous drinking over 2 days)?

Duration of longest binge?

Were you drinking heavily in the last year before you became ill?

CAGE Questions (where alcoholism suspected)

- Have you ever felt you needed to Cut down on your drinking?
- Have people Annoyed you by criticizing your drinking?
- Have you ever felt Guilty about drinking?
- Have you ever felt you needed a drink first thing in the morning (eye-opener), to steady your nerves, or to get rid of a hangover?

DRUG HISTORY

Have you every used or experimented with any of the following drugs? At what age did you start?

DRUG DESCRIPTION		
Cannabis	0/1/2/3	Age .....
Heroin (iv)	0/1/2/3	Age .....
Opiates (non iv)	0/1/2/3	Age .....
Ecstasy	0/1/2/3	Age .....
Cocaine	0/1/2/3	Age .....
Magic Mushrooms	0/1/2/3	Age .....
LSD	0/1/2/3	Age .....
SPEED	0/1/2/3	Age .....
Solvents	0/1/2/3	Age .....
Downers		
Benzodiazepines	0/1/2/3	Age .....
Barbiturates	0/1/2/3	Age .....

(0=never, 1=once or twice, 2=frequent, 3=regular)

Use is a typical week during the last month? _____

Use in a typical week during the last year? _____

Been in touch with psychiatric services or your doctor for your nerves, drug or alcohol advice	YES/NO	YES/NO
If yes, please give details		
Are you taking prescribed medication?	YES/NO	YES/NO
If yes, please give details		

Comorbidity:

Are you aware of any (other) health problems which might be affecting your general well-being on a daily basis?

e.g. **Diabetes?**

- do you know of any close relatives who have diabetes?

e.g. **High Cholesterol?**

e.g. **Thyroid Problems?**

e.g. **Epilepsy?** (go to page 7)

Side effects?

Date *started* to be taken regularly (at least 75% compliant):_____

Current meds – time of day and how much? _____

Is this what you have done all along? (if not, why?) _____

Antipsychotic (s)	Dose	Date prescribed	Date *started* to be taken regularly (at least 75% compliant)

DSM4 Diagnosis:

Age of Onset: **First psychiatric symptoms:** _____
First positive psychotic symptoms: _____
First psychiatric hospitalisation: _____

Other admissions?

See Nottingham Onset Scale

Special Education: **y/n**
Special Education due to low IQ **y/n**
Special Education for maths **y/n**

Neurological History
History of fits: 0 = no; 1=yes
Age of first fit……..
Age of last fits ……
Number of fits ……
Neurological Disorder 0=no; 1=yes

Neurological Illness
Head injury leading to hospital admission: 0=no; 1=yes
No of head injuries: ……..
Intracranial Infection e.g. Meningitis: *0=no; 1=yes*

MEDICATION
Age started psychiatric medication _____

Age started antipsychotic medication _____

Present Psychiatric Medication:

Past Medication Antipsychotics: (type and length)

Antidepressants (type and length):

Mood stablisers (type and length):

Anxiolytics (type and length):

Other (type and length):

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Footnote:
Participants did not see this list of "pro forma" questions. Some questions were not routinely asked, for example, participants were not expected to know dates relating to illness onset or medication details which, in any case, would be checked. A question about parental occupations was dropped at the first interview.

Safety Questionnaire for MRI

SAFETY QUESTIONNAIRE FOR MRI
(Initial Screening Only)

Surname …….. First Names ……

Date of Birth ……

Name of GP or Surgery …….

(Please circle correct response)

1. Have you had any Scans or X-rays here /at King's before?	Y/N
2. Do you have a pacemaker or artificial heart valve fitted?	Y/N
Any other heart or chest operations?	Y/N
3. Have you had any operations on your head, ears or spine?	Y/N
4. Have had any operations where metal might have been inserted into your body and left there? If 'Y', please give details ……	Y/N
5. Do you have any metal in your eyes? Have you done any welding or metalwork? Do you have any shrapnel in you body?	Y/N Y/N Y/N
6. Do you have any the following: Dentures, dental plates or bridges? Y/N — False limb, caliper or brace? Tattoos / metallic make-up? Y/N — Hearing aid or ear implant? Body Piercings? Y/N — Intra-uterine device?	 Y/N Y/N Y/N
7. Do you have a history of (a) Seizures (b) Diabetes (c) Allergic reaction to drugs? If so, please state which drugs ……	Y/N Y/N Y/N
8. Is there a chance you might be pregnant?	Y/N
9. Do you have any history of any problems with your heart or arteries?	Y/N
10. Do you have a history of kidney problems?	Y/N
11. Are you able to lie flat without becoming breathless?	Y/N
12. How much do you weigh? (write "approx" if unsure) …… How tall are you? ……	

Today's Date ……

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